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TUMORS OF THE LOWER RESPIRATORY TRACT

Averill A. Liebow, M.D.

ARMED FORCES INSTITUTE OF PATHOLOGY

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ATLAS OF TUMOR PATHOLOGY

Section V—Fascicle 17

TUMORS OF THE LOWER RESPIRATORY TRACT

by

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ATLAS OF TUMOR PATHOLOGY

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TUMORS OF THE LOWER RESPIRATORY TRACT

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TUMORS OF THE LOWER RESPIRATORY TRACT

INTRODUCTION

Better understanding of the physiology of the thorax and its contents led to positive pressure anesthesia, whereby the lungs became as readily accessible to surgical intervention as the abdominal viscera. Knowledge of the natural history of intrathoracic tumors has, therefore, assumed an immediate practical importance demanding rapid development.

These neoplasms comprise a complex group whose classification is still controversial. Often a clear distinction cannot be made between tumors of bronchial and parenchymal origin. Furthermore, atypical proliferative processes merge gradually into neoplasms. The table of contents of this fascicle represents a classification made because of the necessity of taking a stand, vulnerable as it may be. The most controversial of these groupings are the tumors classified under adenoma of the bronchus and bronchiolar carcinoma, and the primary tumors of the pleura. The tumors grouped under adenoma of the bronchus are by some classified as adenocarcinomas of low malignancy. Pulmonary adenomatosis often is considered a benign entity separate from bronchiolar carcinoma, but is here classified as a variant of bronchiolar carcinoma. In the controversy over whether or not localized or diffuse pleural tumors are derived from the lining mesothelial cells, the stand is taken that such tumors do exist but are rare and should be diagnosed with caution.

Nomenclature for Bronchi and Lung Segments

Accurate localization of lesions is important in recording facts that may contribute to an understanding of the natural history of pulmonary disease. The segments into which the lung may be divided are bronchovascular units that may often be approached individually in resective surgery. The Jackson-Huber nomenclature for these segments (fig. 1) is generally satisfactory and has now become the accepted standard. It will be employed in the subsequent pages.

Obstruction of the Bronchus

The clinical symptoms of benign or malignant endobronchial tumors are primarily due to the mechanical effects of partial or complete obstruction of an expanding and contracting airway. Tumors of the parenchyma when located near a major bronchus or tumors involving hilar lymph nodes may produce similar effects by external pressure on the bronchus. The physiologic mechanisms involved with abundant illustrative clinical and pathologic material are extensively discussed by Jackson and Jackson.

NOMENCLATURE OF BRONCHI AND LUNG SEGMENTS

Figure 1. The labelled subdivisions on the diagram are segments of the lung. Each bronchial branch is named to correspond with the segment of lung which is indicated by the same type of stippling and crosshatching. This nomenclature has been widely accepted and is that suggested by Jackson and Huber. (Jackson, C. L., and Huber, J. F. "Correlated applied anatomy of the bronchial tree and lungs with a system of nomenclature." Dis. of Chest, 9: 319–326, 1943. This illustration is similar to figure 2 and a portion of Plate I in their article.) A. F. I. P. Acc. No. 218737–278.

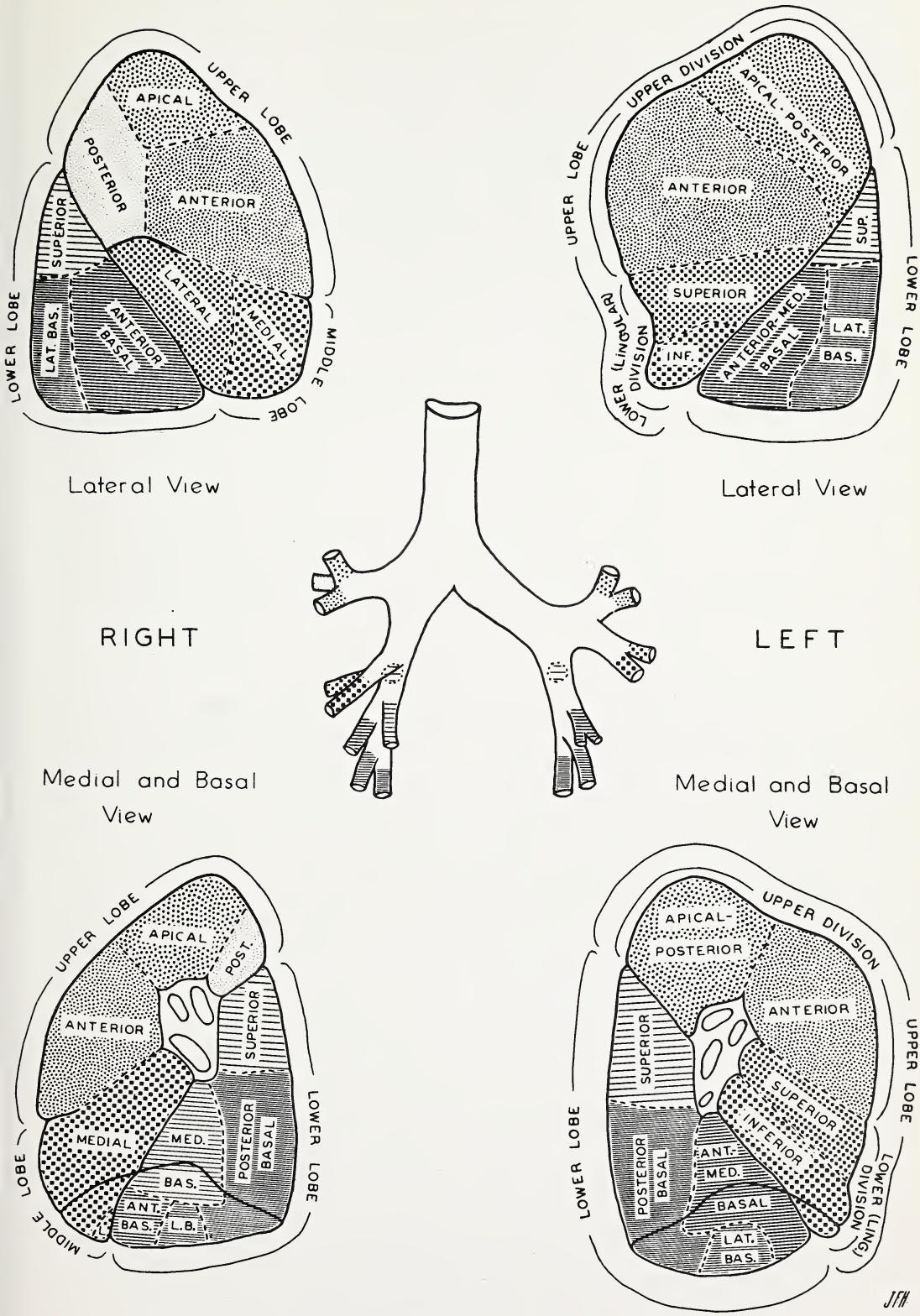
UPPER LOBE
APICAL
POSTERIOR
ANTERIOR
SUPERIOR
LATERAL
MEDIAL
ANTERIOR BASAL
LAT. BAS.
LOWER LOBE
MIDDLE LOBE
Lateral View
UPPER LOBE
UPPER DIVISION
APICAL-POSTERIOR
ANTERIOR
SUP.
SUPERIOR
LOWER (LINGULAR) DIVISION
INF.
ANTERIOR MED. BASAL
LAT.
BAS.
LOWER LOBE
Lateral View
RIGHT
LEFT
Medial and Basal View
Medial and Basal View
UPPER LOBE
APICAL
POST.
ANTERIOR
SUPERIOR
MEDIAL
MED.
POSTERIOR BASAL
BAS.
ANT.
BAS.
L.B.
LOWER LOBE
MIDDLE LOBE
UPPER DIVISION
APICAL-POSTERIOR
ANTERIOR
SUPERIOR
SUPERIOR
INFERIOR
ANT.-MED.
POSTERIOR BASAL
BASAL
LAT.
BAS.
LOWER (LING.) DIVISION
UPPER LOBE
LOWER LOBE
JFH

Fig. 1

ATYPICAL PROLIFERATION

(Figures 2 and 3 are from the same case)

Figure 2. Proliferated squamous epithelium at the margin of an infarct of the lung. The squamous cells seem to fill the lumina of the branches of a bronchiole associated with the occluded artery. × 27. A. F. I. P. Acc. No. 218737–80.

Figure 3. Detail of squamous epithelium in figure 2, showing keratinization. × 170. A. F. I. P. Acc. No. 218737–81.

Figure 4. Proliferated epithelium probably of mucous glands in the wall of a bronchiectatic sac. These cells resemble those seen in certain bronchial adenomas. × 150. A. F. I. P. Acc. No. 218737–82.

Figure 5. Proliferated epithelium probably of a remnant of a mucous gland in the wall of a bronchiectatic sac. × 150. A. F. I. P. Acc. No. 218737–83.

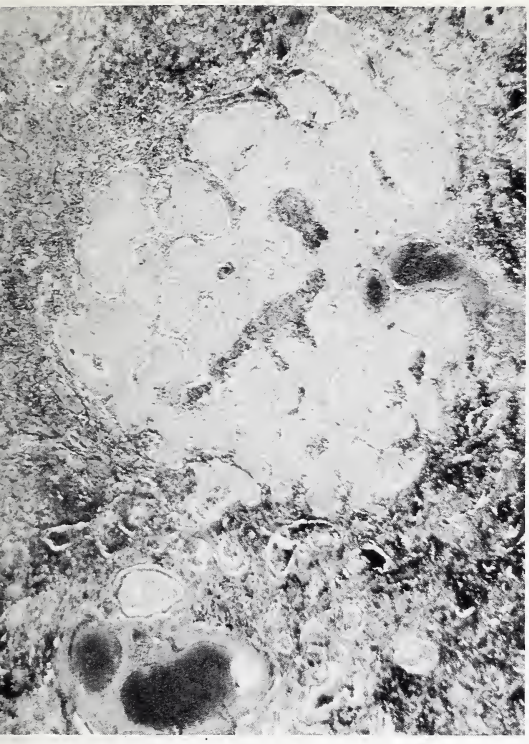

Fig. 2

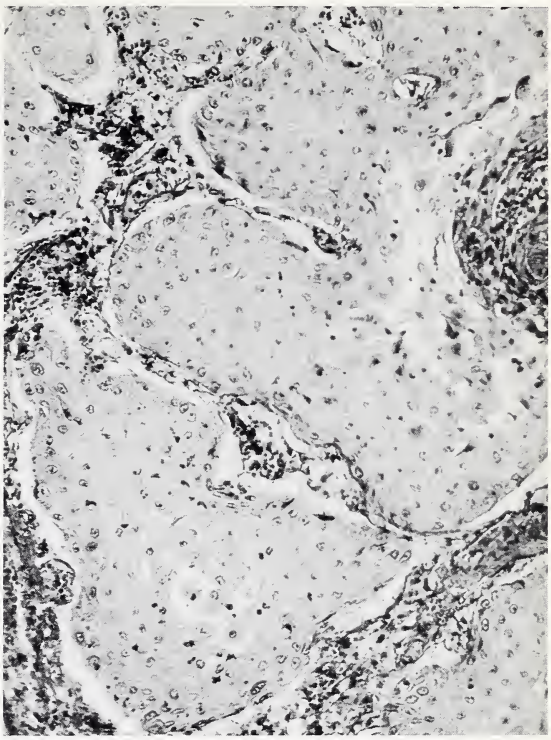

Fig. 3

Fig. 4

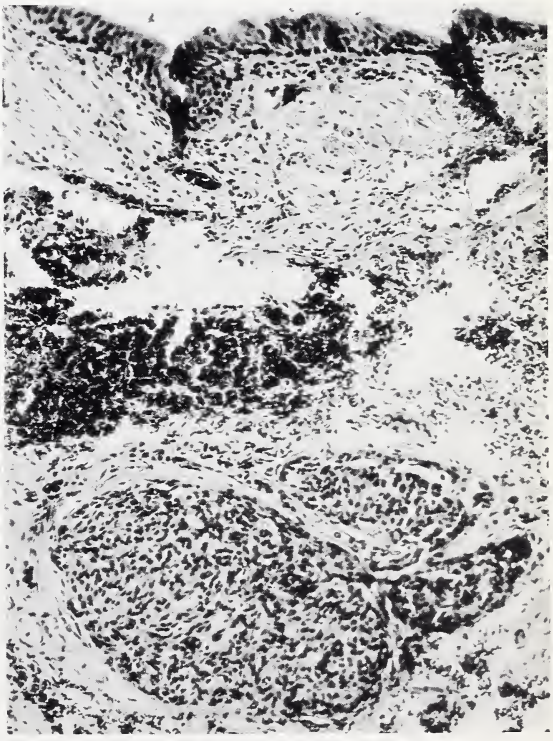

Fig. 5

ATYPICAL PROLIFERATION

Figure 6. Regeneration of cells lining alveolar spaces. Lining of bronchiole continuing as non-ciliated cuboidal epithelium into smaller spaces. The latter cannot be identified as the original alveoli. A. F. I. P. Acc. No. 218737-84.

Figure 7. Epidermidization of lining of alveolar duct. Note also the proliferation of the cuboidal cells adjacent to the areas of squamous metaplasia. × 200. A. F. I. P. Acc. No. 218737-42.

Figure 8. Atypical proliferation in organizing pneumonia. Very atypical cells line the terminal respiratory passages. Such cells when seen in smears from sputum can easily be confused with those desquamated from a malignant neoplasm. × 270. A. F. I. P. Acc. No. 218737-59.

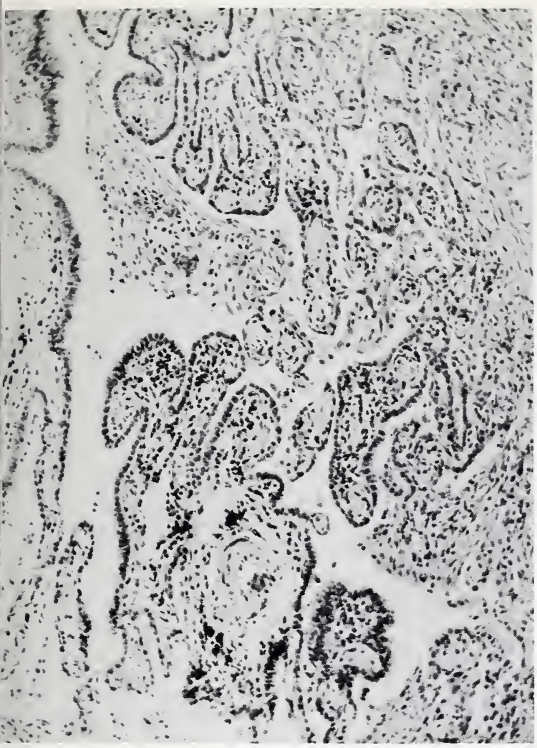

Fig. 6

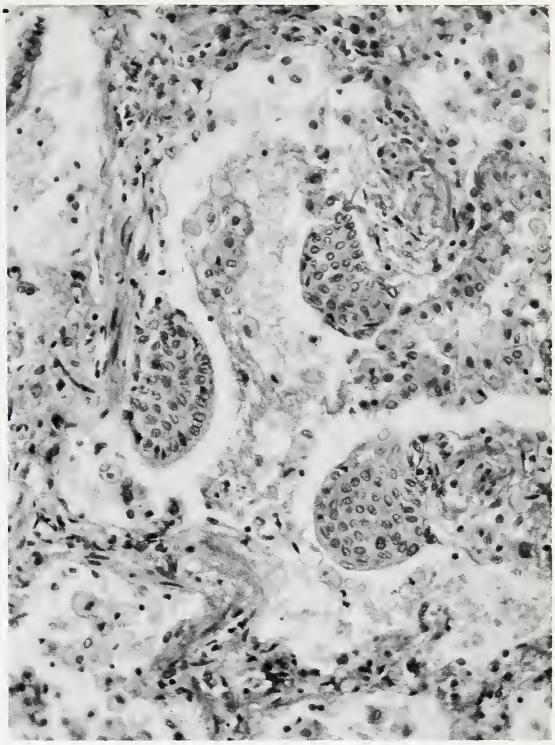

Fig. 7

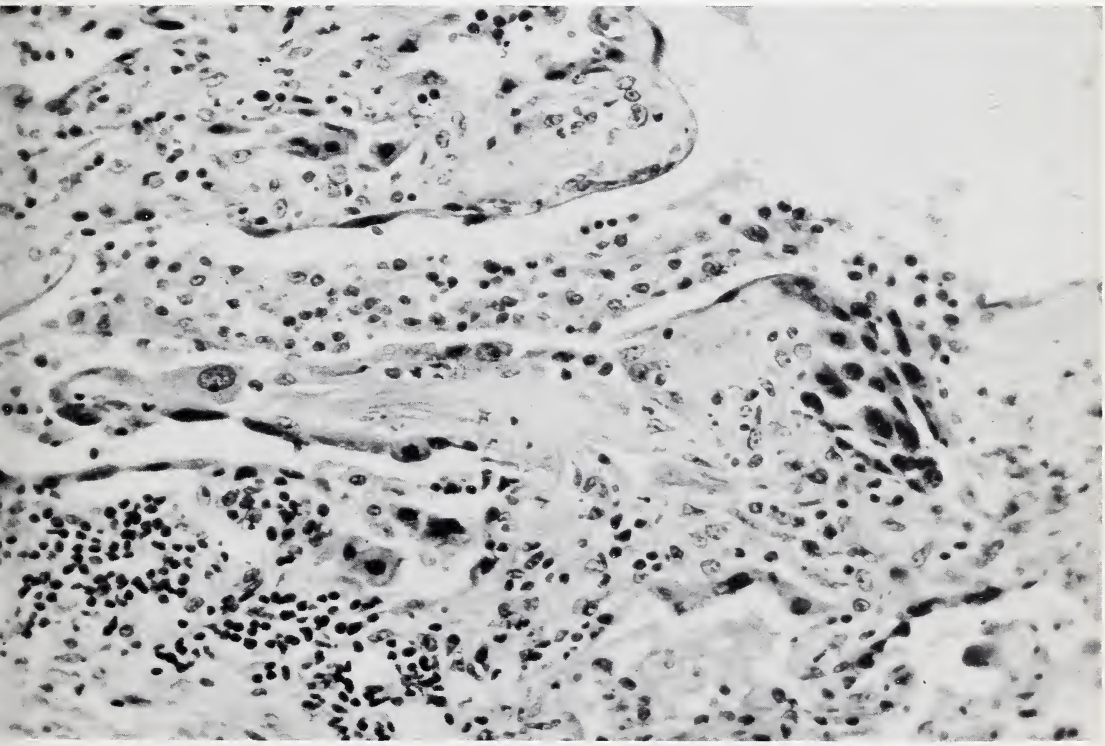

Fig. 8

ATYPICAL PROLIFERATION

(Figures 9–11 are from the same case*)

Figure 9. Proliferation of cells lining peripheral air passages. This small subpleural lesion was an isolated incidental finding in the lungs of a 69-year-old woman. A bronchiole (see higher magnification in figure 10) leads into a labyrinth, lined in part by attenuated alveolar walls and in part by very tall mucus-producing cells (see higher magnification in figure 11) supported upon thick walls of connective tissue. The appearance is similar to that seen in the histologically benign forms of bronchiolar carcinoma. A. F. I. P. Acc. No. 218737–85.

Figure 10. Detail of figure 9. The entering bronchiole is lined by ciliated low columnar epithelium (lower half of picture), changing distally (upper half of picture) to taller mucus-producing cells. A. F. I. P. Acc. No. 218737–86.

Figure 11. Detail of figure 9. A portion of the labyrinth showing the lining tall columnar epithelial mucus-producing cells. Numerous lymphocytes are found in the connective tissue stroma. Compare with figures 62 and 63. A. F. I. P. Acc. No. 218737–87.

*Available through the courtesy of Dr. Roy Barnett, Norwalk, Conn.

Fig. 9

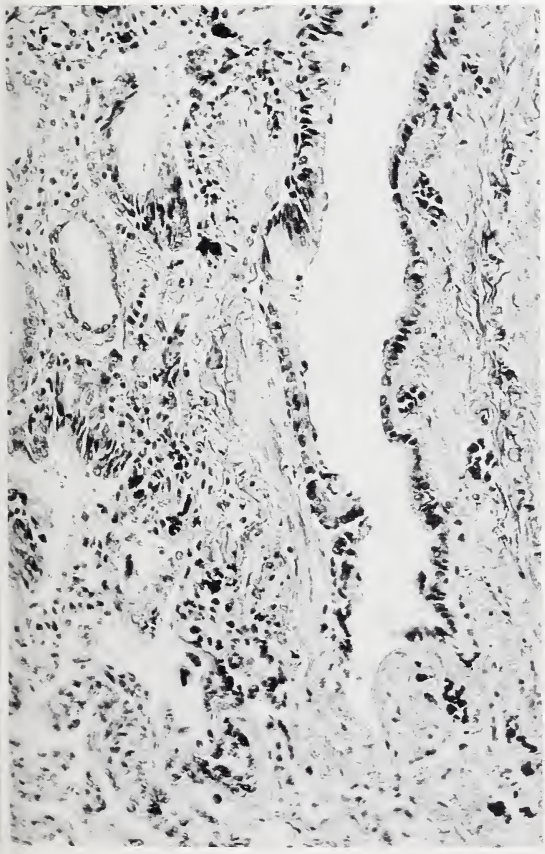

Fig. 10

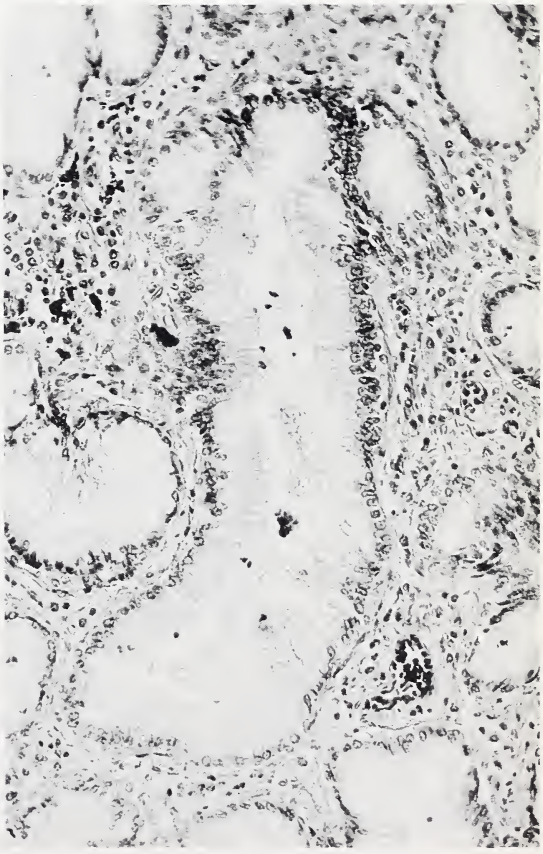

Fig. 11

Symptoms of obstruction are accentuated by intercurrent respiratory infections of the tract, which tend to be localized in the segments of lung distal to the obstruction. In such cases the more obvious signs of pulmonary infection may mask the diagnosis of tumor and cause delay in radical treatment.

The final phase is that of complete obstruction of the airway with a stop valve action. This is invariably associated with purulent inflammation of the lung parenchyma distal to the obstruction either in the form of abscess or bronchiectasis.

Atypical Proliferation

Metaplastic proliferative changes and regenerative hyperplasia occur frequently in the lung and merit brief discussion before truly neoplastic processes are considered, since it may be difficult to distinguish them.

Squamous epithelium commonly lines bronchi in chronic bronchitis and bronchiectatic sacs, walls of abscesses, and tuberculous cavities where there has been regeneration. Squamous epithelium tends to persist when infection persists, but is replaced by tall ciliated epithelium when healing becomes complete. Proliferation of squamous epithelium in the bronchi or bronchioles may be exuberant as at the margins of infarcts (figs. 2, 3) or in organizing pneumonitis. It is noted, for example, in the postinfluenzal pneumonias. For reasons to be outlined in the discussion of etiologic factors in carcinoma of the lung, it is doubtful that such zones of metaplasia often give rise to carcinoma of the lung. Yet, when such squamous metaplasia is found in a bronchoscopic biopsy the patient should be carefully followed.

Metaplastic changes may occur also in the mucous glands and their ducts. They may come to be lined by flattened cells or occasionally by proliferated cuboidal or cylindric cells resembling those of the "carcinoid" form of bronchial adenoma (figs. 4, 5).

In disease extremely bizarre cells may come to line the terminal air passages (figs. 6–8). Their origin—whether from pre-existing lining cells of the alveoli, from downward proliferation of the epithelium of bronchioles or alveolar ducts, or from transformation of mesodermal "septal cells"—is in dispute. This problem has been discussed by Watts and McDonald who came to the conclusion that both septal cells and basal cells from the bronchi proliferated to line alveoli. Some of these cells may exhibit a capacity for phagocytosis. In preparations of sputum these bizarre cells may be interpreted as tumor cells and account for some of the errors in cytologic diagnosis of carcinoma of the lung.

Rarely tall nonciliated mucus-producing cells may come to replace the epithelium of bronchioles and to extend peripherally as a sheet into the alveoli themselves. The resemblance of this process to the fundamental change in certain instances of bronchiolar carcinoma is striking (figs. 9–11).

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PAPILLOMA OF THE BRONCHUS

(Figures 12 and 13 are from the same case)

Figure 12. Papilloma of subsegmental bronchus. The tumor is attached just beyond a point of branching. Most neoplasms of this type occur at or close to the bifurcation of the trachea. × 10. (From the Armed Forces Institute of Pathology.) A. F. I. P. Acc. No. 16717–1.

Figure 13. Enlargement of portion of figure 12. Base of tumor showing only slightly atypical, in part keratinized, squamous epithelium. There is no evidence of invasion of the wall of the bronchus. × 75. (From the Armed Forces Institute of Pathology.) A. F. I. P. Acc. No. 16717–2.

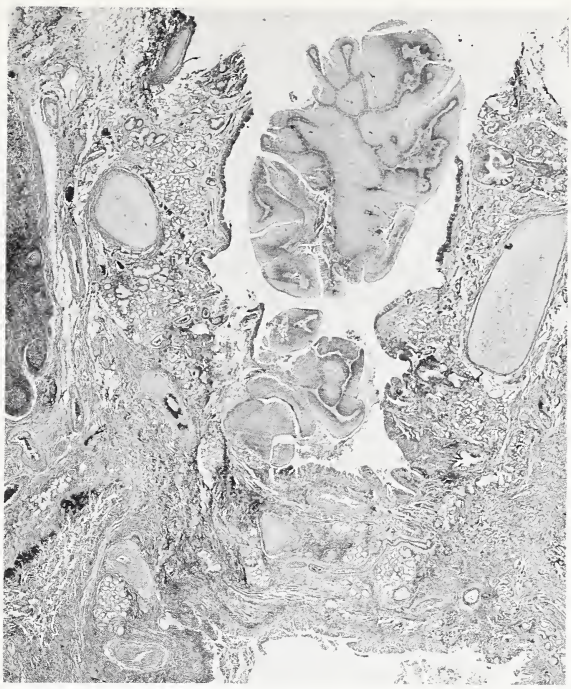

Fig. 12

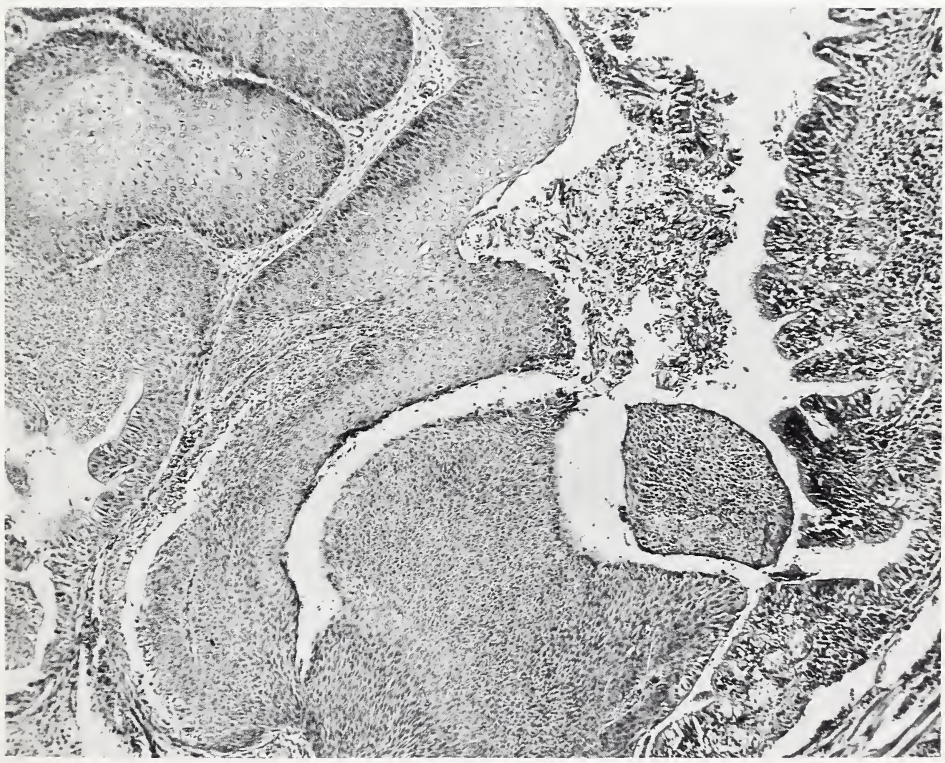

Fig. 13

PAPILLOMATOSIS OF THE BRONCHI

(Figures 14–21 are from the same case*)

Figure 14. Roentgenogram of the thorax shows multiple cystic areas. × 55. A. F. I. P. Acc. No. 218737–296.

Figure 15. Autopsy specimen of lungs which have been transected in a frontal plane and a portion reflected laterally as a flap on each side. There is papillomatous transformation of the mucous membrane of the larynx and contiguous tissues and of the entire tracheobronchial tree, with partial obstruction. In the periphery the transformed bronchi open into cavities, some of very large size, lined by sheets of squamous, or ciliated, or metaplastic columnar or cuboidal epithelium. Irregular warty masses project into these cavities in many places. There are also minute, peribronchiolar, pearly masses that microscopically are made up of squamous epithelium (figs. 20, 21). The specimen was from an 8-year-old negro female child who at the age of four and one-half years developed hoarseness progressing to aphonia and dyspnea. Even though squamous papillomas were repeatedly removed from her larynx and pharynx, she needed a tracheotomy tube for adequate exchange of air. Seven months before death, X-ray of the chest (see figure 14) showed multiple cystic areas. She died in acute respiratory failure following attempted thoracentesis of what was interpreted at fluoroscopy as a pleural fluid level. A. F. I. P. Acc. No. 218737–278.

*Case of Dr. John Kirchner, New Haven, Conn.

Fig. 14

Fig. 15

PRIMARY TUMORS OF THE BRONCHI AND LUNGS

EPITHELIAL TUMORS

Papilloma and Papillomatosis of the Bronchial Tree

This is a benign lesion consisting of folds of connective tissue supporting stratified cuboidal or squamous epithelium.

The papillomas of the bronchus are remarkable in that they are relatively common in the extremely young. They occur predominantly at the mouths of the stem bronchi, often straddling the carina, and may be multiple. Some, however, occur in the segmental bronchi (fig. 12). The lesion may, very rarely, be diffuse with involvement of the larynx and associated tissues, as well as of the entire tracheobronchial tree (fig. 15).

GROSS. The lesion resembles papilloma as seen commonly in the larynx. It consists of sessile, polypoid, cauliflower-like or fissured masses that spring from the mucous surface and restrict the lumen of the airway. In multiple papillomatosis the bronchi may be expanded distally into cavities lined by metaplastic epithelium from which there are papillomatous projections. Even the smallest bronchioles may be involved (fig. 15).

MICROSCOPIC. Small regularly arranged cells, intermediate in type between the columnar epithelial cells and the squamous elements, form the bulk of the tumor. At the centers of the epithelial cell masses, the cells are definitely squamous with a tendency toward keratinization (fig. 13). Thin highly vascular laminae of connective tissue spring from the mucous membrane of the bronchus (figs. 12, 13). There is no extension between the cartilages.

The pathogenesis of these lesions is of interest. In the diffuse form there is evidence of gradual transitions from ciliated columnar epithelium to metaplastic cuboidal epithelium, and to squamous epithelium, suggesting an origin in situ at many points (figs. 16–19). The appearance of the bronchiolar and peribronchiolar lesions, however, suggests that there may also be aspirative implantation (figs. 20, 21).

From their position, as well as from the absence of invasion, the localized tumors are subject to bronchoscopic removal. There is no available evidence that the papillomas may undergo carcinomatous change. They may, however, recur.

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PAPILLOMATOSIS OF THE BRONCHI

(Figures 14–21 are from the same case*)

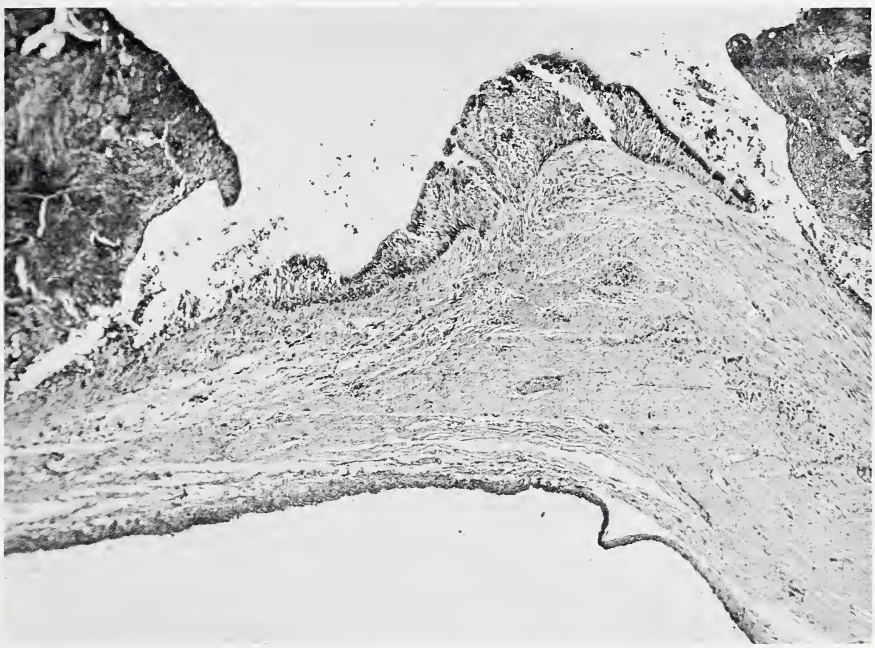


Fig. 16

Figure 16. Histologic section of one of the cavities in the lungs seen in figure 15. In part it is lined by ciliated columnar epithelium underlain, in part, by a cushion of metaplastic epithelium. Near each margin of the photograph a large papillomatous mass, continuous with the epithelium of the surface, projects far into the lumen of the cavity that has been formed. × 55. A. F. I. P. Acc. No. 218737–294.

*Case of Dr. John Kirchner, New Haven, Conn.

PAPILLOMATOSIS OF THE BRONCHI

(Figures 14–21 are from the same case*)

Figure 17. The ciliated epithelium of the surface is elevated by a localized plaque of epidermoid epithelium suggesting for the latter an origin in situ. × 145. A. F. I. P. Acc. No. 218737–293.

Figure 18. The lining epithelium becomes continuous with the bulk of a papillomatous mass that projects into the cavity of an expanded bronchus. × 145. A. F. I. P. Acc. No. 218737–290.

Figure 19. One of the large cavities, such as are demonstrated in figure 15, is seen to have a thick wall composed of interdigitating masses of squamous epithelium. × 55. A. F. I. P. Acc. No. 218737–289.

Figure 20. Low power view of the periphery of the lung showing multiple small masses of squamous epithelium related to the walls of bronchioles, as demonstrated in figure 21. × 12. A. F. I. P. Acc. No. 218737–288.

Figure 21. Enlarged view of the small mass shown nearest the right hand margin of figure 20. Here squamous epithelium appears to have replaced a part of the lining membrane of a bronchiole, and expands into the surrounding alveoli. This appearance could be given by the growth of an aspirated epithelial fragment. × 145. A. F. I. P. Acc. No. 218737–287.

*Case of Dr. John Kirchner, New Haven, Conn.

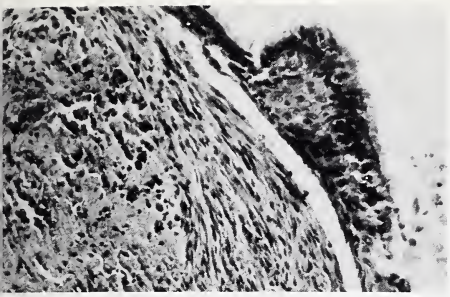


Fig. 17

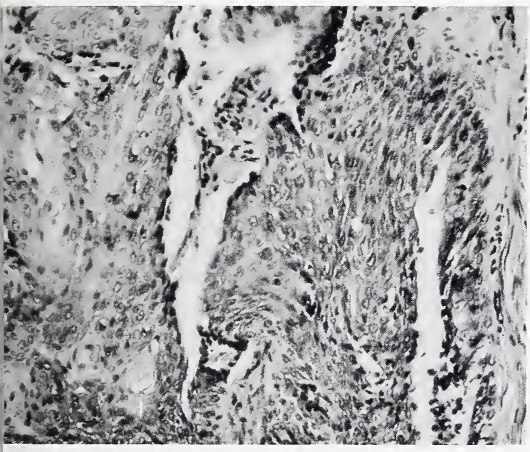


Fig. 18

Fig. 19

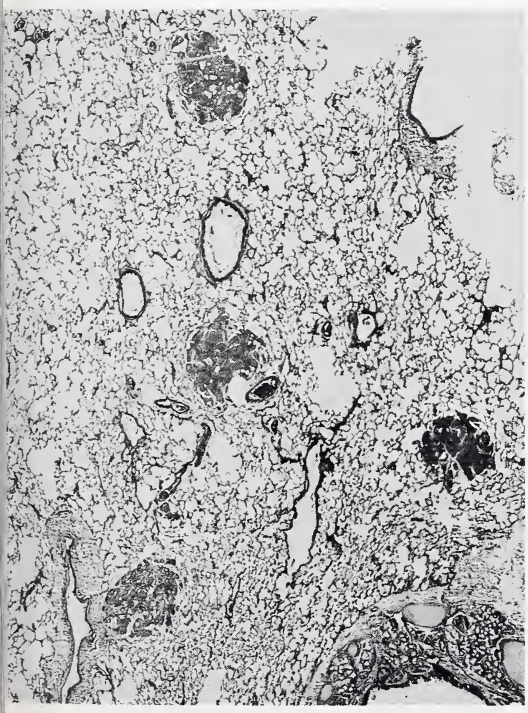


Fig. 20

Fig. 21

Adenoma of Bronchus

SYNONYMS AND RELATED TERMS:* Adenoma bronchi (Lat.); adenocystic basal cell carcinoma; adenoid basal cell carcinoma of bronchus; adenomatoid tumor of bronchus; "adenomatous polyp"; "anlage and rest tumor"; "basal cell carcinoma"; benign glandular bronchiogenic tumor; benign glandular tumor; bronchial adenoma; "bronchial paraganglioma"; "carcinoid"; "collar button lesion"; "cylindroid"; "cylindroma"; "endothelioma"; "epithelioma adenoides cysticum"; malignant adenoma; "mixed salivary gland tumor"; mixed tumor; muco-epidermoid tumor; "oncocytoma"; "polyp"; polypoid adenoma; "polypoid bronchial tumors"; reserve-cell tumor; vascular adenoma.

Under the designation adenoma of bronchus are included slowly growing, at first circumscribed but later sometimes invasive or sluggishly metastasizing, polypoid or sessile, epithelial neoplasms involving the subepithelial tissues, usually of proximal bronchi. The term adenoma of the bronchus is retained for this group of tumors, despite their ability on occasion to invade and metastasize, since the term is in common usage and since the behavior of these tumors when they do invade and metastasize is so strikingly different from that of the more common bronchogenic carcinomas.

These tumors have a well differentiated histologic structure which appears in two characteristic patterns, the carcinoid form and the cylindroid form. The latter may assume an arrangement like that of the basal cell tumor of the skin (fig. 56). A rare variant of the carcinoid pattern is a tumor consisting partially or entirely of oncocytes. (See below, Oncocytoid Variant of Carcinoid Form.) These names are retained because they are currently used. They imply nothing concerning histogenesis. There are some who consider these tumors entirely distinct from each other, but although certain differences do exist, the occurrence of transitional forms as demonstrated by Engelbreth-Holm suggesting a common histogenesis cannot be denied.

The most generally accepted theory of origin, and the one which appears to be best supported, is that the adenomas of all types are derived from the mucous glands and their ducts. Transitions to normal mucous glands may be found both in the carcinoid (fig. 29) and in the cylindromatous form. (See McDonald, Moersch, and Tinney, and case 3 of Engelbreth-Holm.) The existence of oncocytic cell types is compatible with an origin from the mucous glands. The surface epithelium seems a less likely source, since the proliferated tissue is usually separated from it by a well defined band of connective tissue. Origin in the mucous glands also helps to explain the predominant localization in the major bronchi, where mucous glands are relatively abundant, although the mucous glands may be found as far out in the bronchial tree as the cartilages extend, i. e., to bronchi of 1 mm. in diameter.

These tumors do not resemble the salivary gland type of mixed tumors in that there are no myxomatous tissues, no chondroid transformation of epithelium, no stellate elements, and no myoepithelial proliferation. There seems little justification for calling these lesions mixed tumors in the sense of Womack and Graham, thereby implying an organoid, multidermal origin from unde-

*The terms given in this grouping are ones that have been used at one time or another for the lesion under discussion or for one of its variations, and do not necessarily represent current or general usage. Obsolete and undesirable terms are in quotation marks.

veloped anlagen of lung. The common appearance is not that of alveolated tissue, cartilage appears to be engulfed or invaded rather than formed by the tumor, and such bone as is found occurs either from metaplasia of pre-existing cartilage or within the septa or capsule of the tumor. It does not seem to be a part of the neoplastic process.

NATURAL HISTORY, ADENOMAS OF THE BRONCHUS. Bronchial adenomas comprise between 6 and 10 percent of all primary neoplasms of the lung. There is an almost equal incidence in the sexes, in contrast with carcinoma of the lung which occurs five times more frequently in men. Eighty-five percent of the patients are less than 50 years of age, and the average age at the time of treatment is between 35 and 40 years. The average duration of symptoms in a series of patients reported by Moersch and McDonald was 30 months. The age at onset appears to be several years less in the female than in the male. The cylindromas comprise 15 percent of the bronchial adenomas and make their clinical appearance on the average some five years later than the carcinoid adenomas. The oncocytoid tumors appear to occur chiefly in older patients.

The history is that of other slowly growing polypoid tumors of the bronchi, with the difference that their very abundant vascularity makes hemoptysis a prominent symptom. Thus in the report by Moersch and McDonald, dealing with 86 patients, 67 complained of cough, 49 of hemoptysis, and 38 of pain in the chest. When obstruction ultimately occurs, the symptoms are those of the associated, often recurrent, pneumonitis, or, in time, of bronchiectasis.

Recurrence after incomplete operative removal may take place in the hilar stump or in lymph nodes. Many years may elapse before the recurrence becomes clinically manifest, even when it is obvious that tumor has been left behind at operation. In time, however, the growth may on occasion become massive, and the tumor may retain its invasive characteristics, penetrating ultimately beyond the confines of the thorax and about the great vessels in the soft tissues of the neck (figs. 40, 41).

METASTASES, ADENOMAS OF THE BRONCHUS. In a small proportion of cases, tumor cells are found within the bronchial (pl. I–E) or tracheobronchial chains of lymph nodes, or within isolated lymphatics elsewhere in the lymphoid tissues of the mediastinum. This does not necessarily indicate rapid spread. Isolated metastases may occur within the lung of either side (fig. 33). Metastases in the liver, vertebrae, and kidney have also been described, usually in the longer standing cases. However, these tumors rarely kill by metastases. An exceptional instance of death from hepatic insufficiency resulting from metastases of a bronchial adenoma has been reported by Moersch and McDonald.

The cylindroid form of adenoma is more invasive microscopically than the carcinoid form. (See Microscopic, Cylindroid Form.) This might suggest

ADENOMA OF BRONCHUS, CARCINOID TYPE

(Figures 22, 23, and 29 are from the same case)

Figure 22. View into right main bronchus. The tumor projects finger-like into the lumen of the bronchus. Specimen shown in the photograph represents the right lung which had to be removed in its entirety for technical reasons. The patient, a 57-year-old man, had had repeated attacks of pneumonitis for four years before operation. A roentgenogram made two months before operation demonstrated atelectasis of the right upper lobe. A. F. I. P. Acc. No. 218737–97.

Figure 23. Transection of the lung through the base of the tumor, which is located at the orifice of the upper lobe just above the carina at the intermediate bronchus. Note the broad sessile base. The hemorrhage into the protruding end of the tumor is probably associated with a previous biopsy. Bronchiectasis in the lung peripheral to the obstructive tumor was most severe in the posterior segment of the lobe. A. F. I. P. Acc. No. 218737–98.

Figure 24. The surface of the globoid adenoma protruding into the bronchus is smoothly encapsulated by a reflection of the bronchial mucosa. A. F. I. P. Acc. No. 218737–20.

Figure 25. Bronchial cartilages have been surrounded by and embedded within the substance of the tumor. A. F. I. P. Acc. No. 218737–99.

Fig. 22

Fig. 23

Fig. 24

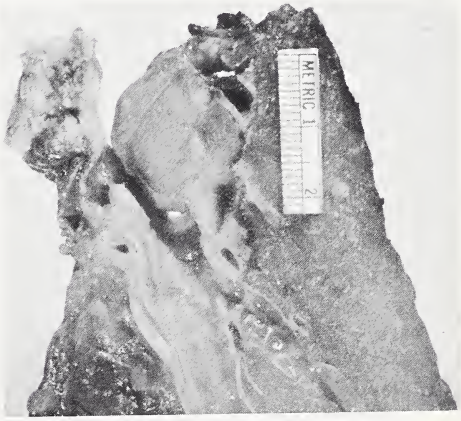


Fig. 25

PLATE I

A.* Adenoma of bronchus, carcinoid type. A globoid mass protrudes into the right main stem bronchus below the right upper lobe orifice. The entire lower lobe was involved in an inflammatory process. The right pneumonectomy was done on a 51-year-old male who, seven years before operation, had had a severe lower respiratory infection lasting six months. Almost two years before operation he had had a second severe lower respiratory infection followed by pneumonia, right pleurisy, fever, chronic productive cough, and occasional blood streaking of sputum. There were two episodes of massive hemoptyses. The diagnosis was made by bronchoscopy and biopsy. A. F. I. P. Acc. No. 218737–262.

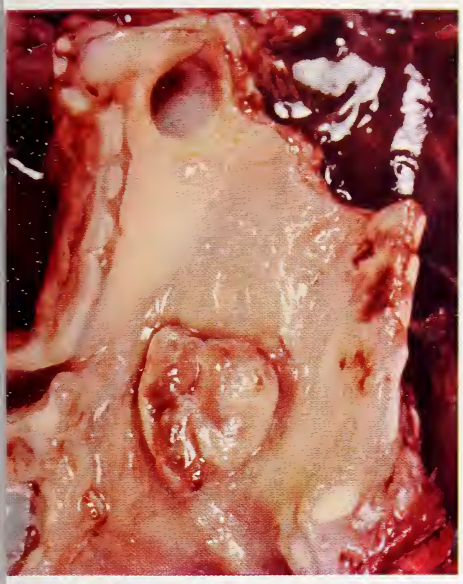
B.* Cut surface of the adenoma shown in plate I–A. Most of the tumor is beneath the surface. It extends for a considerable distance within the lamina propria of the bronchus to the superior segment of the right lower lobe but appears in the gross to be sharply delimited from the substance of the lower lobe. A. F. I. P. Acc. No. 218737–261.

C. Adenoma of bronchus, carcinoid type. This tumor is considered a peripheral adenoma, although near the hilum, since it is not associated with a large bronchus. The histologic appearance of this tumor is shown in figure 37. A. F. I. P. Acc. No. 218737–73.

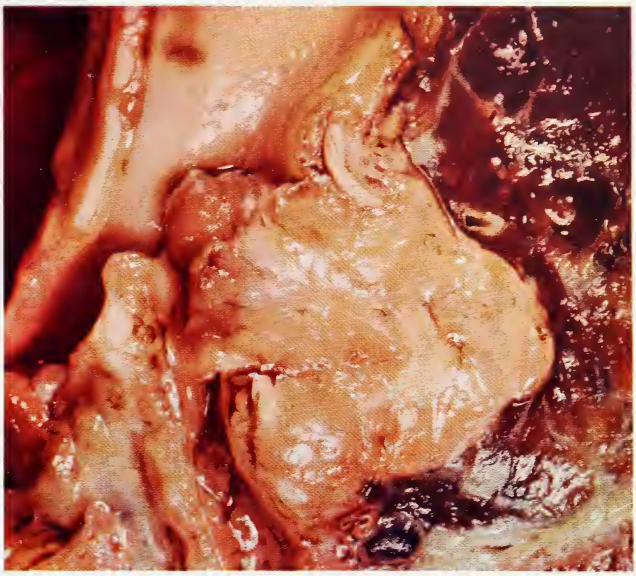
D. Adenoma of bronchus, carcinoid type. The deep portion of a tumor which had only a small intrabronchial protrusion. It is separated by a capsule from the substance of the lung which shows evidence of organizing pneumonitis. A. F. I. P. Acc. No. 218737–17.

E. Adenoma of bronchus, carcinoid type, from the superior segment of the right lower lobe. The necrosis on the surface is uncommon in these tumors. Metastatic tumor is seen in a lymph node in the left lower quadrant of the picture. An isolated, presumably metastatic nodule was seen in the basal segment of the right lower lobe. The histologic section of the isolated nodule is illustrated in figures 33 and 34. A. F. I. P. Acc. No. 218737–33.

*Case presented through the courtesy of Dr. Lauren V. Ackerman. The patient was referred to the service of Dr. Evarts Graham at Barnes Hospital, St. Louis, Missouri, by Dr. Charles G. Blauw, Siloam Springs, Ark.



A



B

C

D

E

PLATE I

that they are more malignant than the carcinoid variety. A review of the available material reveals, however, that only a very few instances of distant metastases of the cylindromatous variety have been reported. More data are needed before the question of the relative malignancy of the carcinoid and cylindroid types can be decided. At present it can merely be stated that the latter shows greater invasiveness.

In these respects—the slow growth and late recurrence, the slight tendency to destroy despite some tendency to invade, and the rare, sluggish, and usually inconsequential metastases—the bronchial adenoma differs markedly from the bronchogenic carcinoma. Death from adenoma is associated with bronchiectasis, pneumonitis, and hemorrhage, with the complications of surgery, or with asphyxia due to obstruction by the tumor mass.

GROSS, CARCINOID FORM. The adenoma projects as a smooth, globoid (figs. 24, 25, 27), or proximally projecting finger-shaped mass (fig. 22) into the lumen of a major bronchus causing partial or complete obstruction (figs. 22–27). At least 90 percent are accessible to the bronchoscope. They are most common on the right side, where they usually occur either in the lower lobe or main stem bronchus. They are least common in the left upper lobe bronchus. Peripherally situated adenomas of the lung are rare, appear to be mainly of the carcinoid type, and may be multiple (figs. 37–39).

There is usually more beneath the surface than can be seen within the bronchus (figs. 25–28, pl. I–A, B, D, E). Only a fourth of these tumors can be considered completely endobronchial, and truly pedunculated forms are uncommon. Rarely, the tumor may reach an immense size externally, while its intrabronchial protrusion remains small. Thus there is almost silent displacement of the thoracic structures with ultimate compression of some vital part (figs. 40, 41). The free surface of the tumor is smooth and covered by a reflection of the bronchial mucous membrane. Ulceration is rare except as a result of biopsy wounds (fig. 28). Because of the great vascularity of these tumors, biopsy may be complicated by considerable or occasionally even fatal hemorrhage. For this reason, some bronchoscopists prefer to rely on gross bronchoscopic diagnosis without biopsy. There is usually a well defined capsule that delimits the lesion from the surrounding tissue (fig. 27, pl. I–D). This capsule is in continuity with the external connective tissue coat of the bronchus. Occasionally, the external surface is bosselated and the capsule may be ill defined over a part or all of the surface as the tumor cells invade the surrounding tissue.

There is considerable variation in color and consistency. The softer tumors (figs. 27, 28) tend to be a pale pink on the cut surface and to be more homogeneous than the firmer lesions (pl. I–D) that tend to resemble the salivary gland or the pancreas in their tan color and subdivision into polygonal lobules by ramifying septa of connective tissue. There is no desmoplastic reaction as there is in many instances of carcinoma. Necrosis is almost never present and then only at the surface when infection has occurred. An unusual example of such necrosis is shown in plate I–E.

ADENOMA OF BRONCHUS, CARCINOID TYPE

(Figures 26 and 27 are from the same case. Figures 22, 23, and 29 are from the same case)

Figure 26. Roentgenogram (laminographic section) of patient whose resected left lung is shown in figure 27. The ovoid mass distorts and greatly narrows the lower lobe bronchus. A. F. I. P. Acc. No. 218737–100.

Figure 27. There is no polypoid protrusion, but the mass lies within the deeper coats of the left lower bronchus whose mucous membrane is intact. The adenoma occupies much of the lower lobe, the remainder of which is the seat of advanced chronic bronchiectasis. A. F. I. P. Acc. No. 218737–101.

Figure 28. Adenoma of bronchus, carcinoid type, in the left lower lobe of the lung. There is bronchiectasis distal to the large soft tumor, and there is massive hemorrhage from the biopsy site. A. F. I. P. Acc. No. 218737–18.

Figure 29. Histologic section of tumor shown in figures 22 and 23. In the upper third of the field, the duct of a mucous gland becomes continuous with a mass of tumor cells. A. F. I. P. Acc. No. 218737–104.

Fig. 26

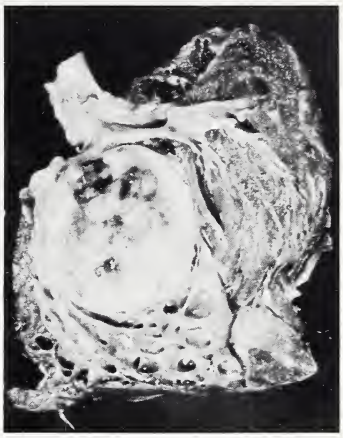


Fig. 27

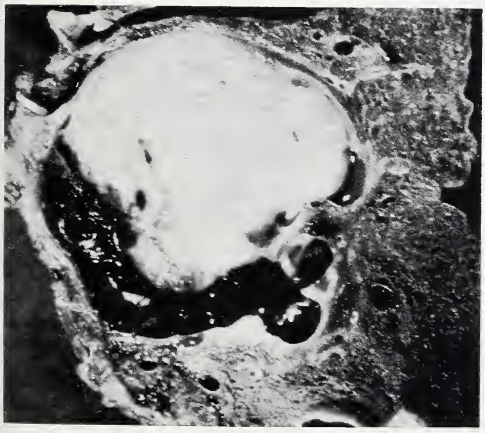


Fig. 28

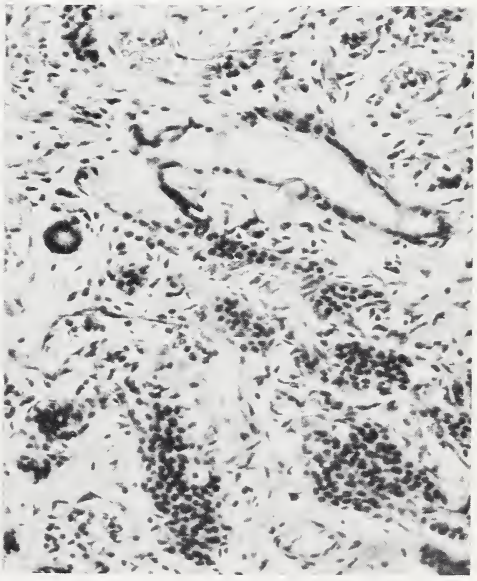


Fig. 29

ADENOMA OF BRONCHUS, CARCINOID TYPE

(Figures 33, 34, and plate I–E are from the same case)

Figure 30. This is a common histologic appearance for these tumors. The stroma is highly vascular. Some of the empty vessels may be lymphatics. × 160. A. F. I. P. Acc. No. 218737–54.

Figure 31. Small groups of tumor cells are seen within the outer portions of the capsule. × 75. A. F. I. P. Acc. No. 218737–35.

Figure 32. True acini as shown in this field are uncommon in the carcinoid type of adenoma. A. F. I. P. Acc. No. 218737–105.

Figure 33. Histologic section of an isolated nodule in the right lower lobe. The nodule is presumed to be a metastasis from the tumor in the superior segment of the right lower lobe illustrated in plate I–E. The acini are lined by somewhat variable and atypical columnar cells. In the primary lesion the tumor had the more characteristic carcinoid structure. A. F. I. P. Acc. No. 218737–106.

Figure 34. Mitosis from portion of tissue shown in figure 33. A. F. I. P. Acc. No. 218737–107.

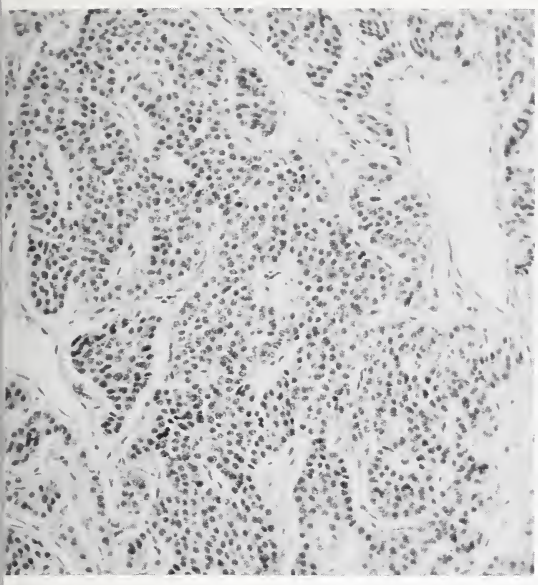


Fig. 30

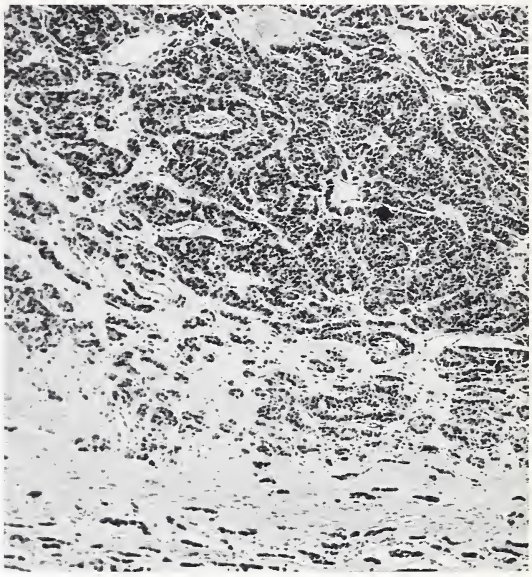


Fig. 31

Fig. 32

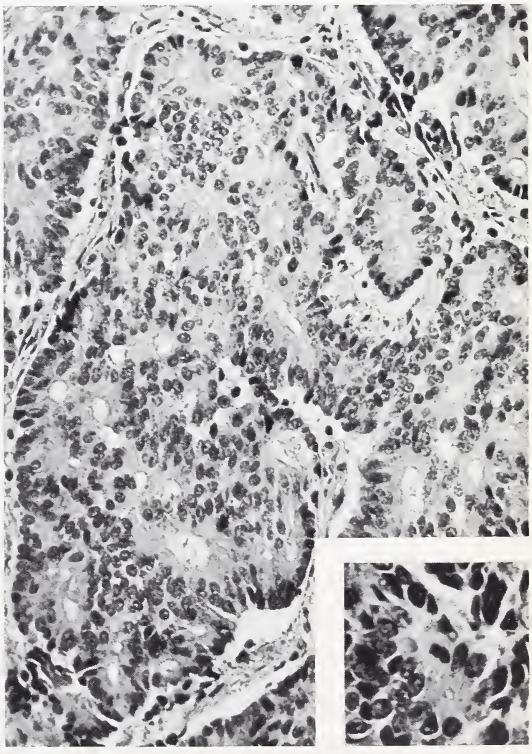


Fig. 33

Fig. 34

ADENOMA OF BRONCHUS, ONCOCYTOID VARIANT OF CARCINOID TYPE

(Figures 35 and 36 are from the same case)

Figure 35. Nodule of cells with the morphology of oncocytes within a tumor of the carcinoid type. A. F. I. P. Acc. No. 218737–34.

Figure 36. Higher magnification of margin of the nodule shown in figure 35. The oncocytes are large pale acidophilic granular cells with nuclei, frequently pyknotic, of variable size. × 250. A. F. I. P. Acc. No. 218737–52.

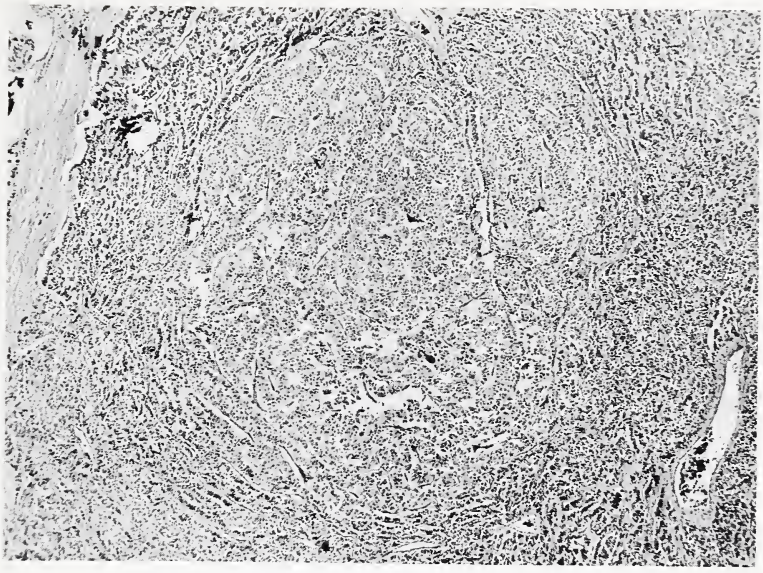


Fig. 35

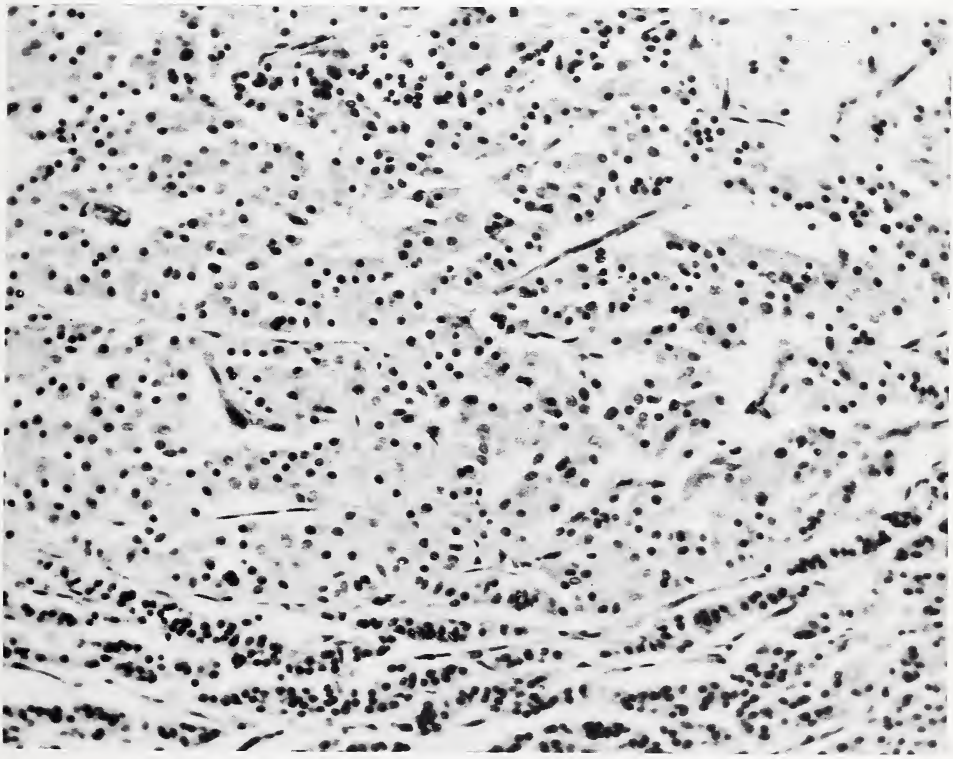


Fig. 36

MICROSCOPIC, CARCINOID FORM. A thin sheet of the bronchial epithelium often showing squamous metaplasia is reflected over the neoplastic tissue. A thickened, reticular basement membrane and a lamina of dense connective tissue intervene between the two (fig. 39). The characteristic cell of the carcinoid type is uniformly small with finely granular acidophilic cytoplasm and nuclei that are finely stippled with chromatin (fig. 30). The resemblance to the carcinoid tumor is indeed remarkable as can be seen by comparison with a pulmonary metastasis of a carcinoid tumor primary in the jejunum (figs. 45, 46). Argentaffine granules have, however, been demonstrated rarely, once in the 34 cases of carcinoid adenomas from a series of 39 bronchial adenomas reported by Holley. Mitoses among these elements are rare (fig. 34). Occasionally, there is a whorling suggestive of squamous transformation. These cells are arranged in sheets and strands, at times in palisades, or more commonly in rounded masses which superficially resemble acinar groupings. True acini, either apparently empty or filled with a nonmucinous, finely granular, protein material, may be encountered, but are uncommon (figs. 32, 33). Characteristically, the cell groups are not in acinar arrangement but are situated about extremely delicate sinusoidal vessels, some filled with blood but others devoid of visible content and probably of lymphatic origin (fig. 30). If very large, the sinusoids dominate the architecture, and such tumors have been mistaken for hemangiomas. Considering these sinusoids, it is not difficult to understand the frequency of hemorrhage. Sometimes the walls of these vessels are thickened by laminae of hyaline collagenous material.

In the invasive tumors of long standing, the cells may be more irregularly arranged in larger masses (figs. 42–44). Although they may vary somewhat more in size and shape, and although occasional mitoses may be in evidence, the fundamental pattern of the encapsulated tumors is nevertheless maintained.

Both of the two truly peripheral adenomas illustrated in figures 37 to 39 are made up of cells that are more granular and vary more in size than in most adenomas. This is, however, within the range of variation encountered in the centrally situated neoplasms. They show the same relation to the lining epithelium of bronchioles that is exhibited by the adenomas in their more usual position within the major bronchi.

Fragments of bone may be found. These appear to be the result of metaplastic changes in the cartilages that become isolated within the tumor, or there is an osseous transformation of the septa or of the capsule. There is no cartilaginous or other transformation of the proliferated epithelial cells such as occurs in the salivary gland type of mixed tumor.

Permeation of the capsule by tumor cells occurs in a third to a half of the cases (fig. 31). Vascular invasion and perineural lymphatic extension have been observed. Cartilage may be invaded although this appears to be more common in the cylindroid variety (fig. 54). Groups of tumor cells may even be seen in the marrow of metaplastic bone within the invaded cartilage.

ADENOMA OF BRONCHUS, CARCINOID TYPE

(Figure 37 and plate I–C are from the same case. Figures 38 and 39 are from the same case)

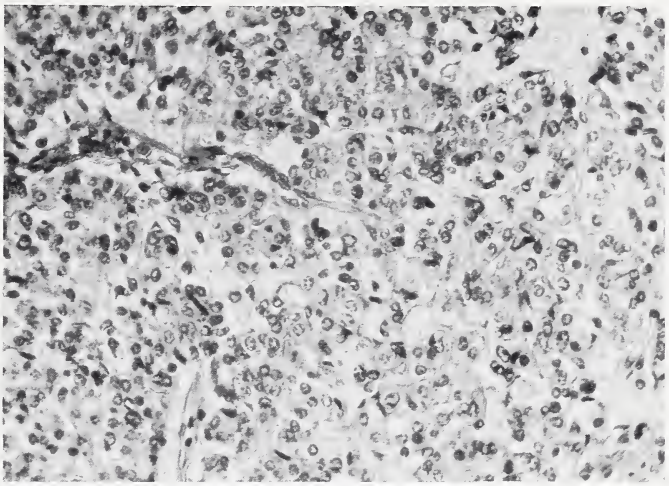


Fig. 37

Figure 37. Histologic section from the peripheral adenoma in plate I–C. The cells are more granular and possess large, somewhat more variable nuclei than most bronchial adenomas of the carcinoid type. A. F. I. P. Acc. No. 218737–109.

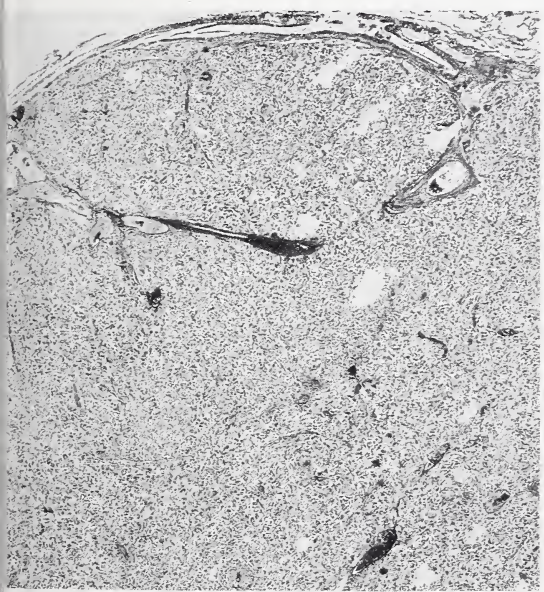


Fig. 38

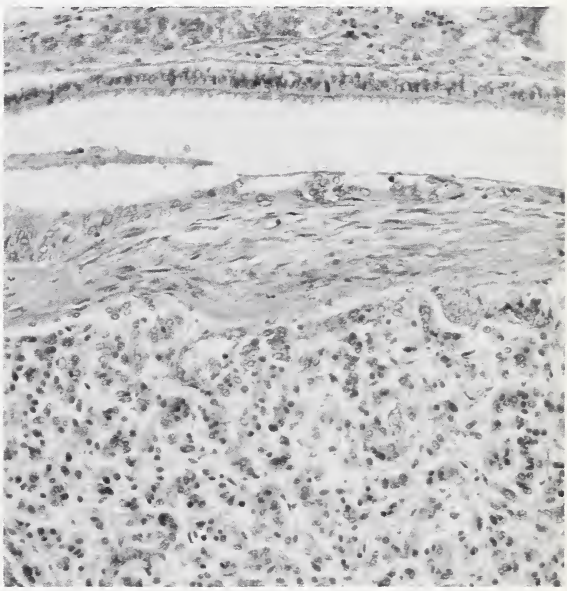


Fig. 39

Figure 38. This tumor is one of two peripheral adenomas found incidentally at necropsy. × 21. A. F. I. P. Acc. No. 218737–64.

Figure 39. Detail of figure 38. There is squamous metaplasia of a part of the lining epithelium of the bronchiole which is separated from the tumor cells by a lamina of connective tissue. The resemblance of the cells to those of the tumor shown in figure 37 is striking. × 160. A. F. I. P. Acc. No. 218737–41.

ADENOMA OF BRONCHUS, CARCINOID TYPE

(Figures 40–44 are from the same case)

Figure 40. Anterior view of an adenoma of the bronchus, carcinoid type, invading the mediastinum by direct extension. This specimen was obtained post mortem from a 53-year-old man. Four years previously he had complained of hoarseness, and indirect laryngoscopy demonstrated paralysis of the left vocal cord. There was no sputum. At that time there was already evidence of a large mediastinal mass in the roentgenogram. A diagnosis of "anaplastic carcinoma" was returned after microscopic examination of a specimen obtained at mediastinotomy. There was only slight decrease in the size of the tumor after massive irradiation in 1942 and again in 1945. In September 1946 a mass partly occluding the left main bronchus was observed bronchoscopically. A biopsy did not reveal tumor. An enlarged left supraclavicular node was removed and the pathologic diagnosis of "bronchial adenoma with some anaplastic change" was made. The patient died in November 1946 after progressive dyspnea and cyanosis. A. F. I. P. Acc. No. 218737–110.

Figure 41. Close-up of transverse section across left main bronchus. There is elevation of the mucous membrane of the bronchus by tumor tissue along the posterior wall, producing a bulge into the lumen. Elsewhere the growth of the neoplastic tissue was extrinsic. Several lymph nodes permeated with tumor tissue are also visible in the section. A. F. I. P. Acc. No. 218737–112.

Figure 42. Histologic section of the tumor shown in figures 40 and 41. The pattern is typical of the carcinoid type of adenoma of the bronchus. Compare with figures 45 and 46. × 85. A. F. I. P. Acc. No. 218737–31.

Figure 43. Histologic section of another area of the tumor shown in figures 40 and 41. The cells are isolated small groups in hyaline connective tissue. Compare with figure 31. Calcification, unusual in adenomas of the bronchus, is probably the result of intensive irradiation of the tumor. A. F. I. P. Acc. No. 218737–32.

Figure 44. Detail of figure 42. The cells in this field are somewhat smaller but not otherwise different from those seen in most examples of the carcinoid type of bronchial adenoma. Small amounts of hyaline connective tissue about the vascular channels are common. × 290. A. F. I. P. Acc. No. 218737–46.

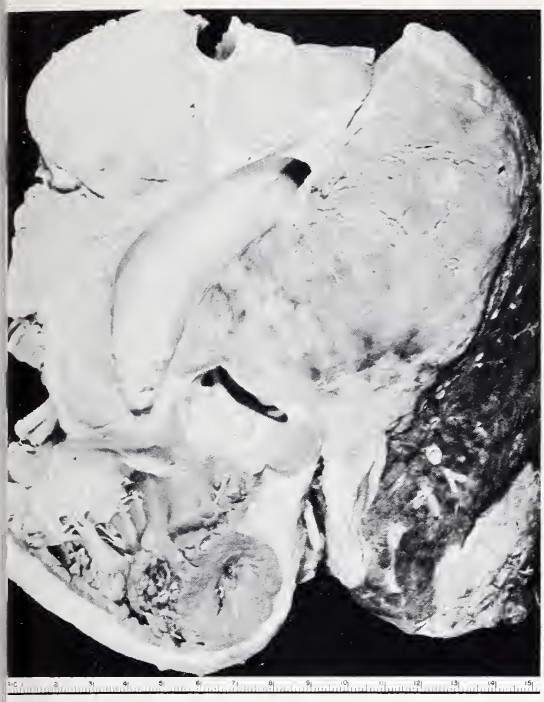


Fig. 40

Fig. 41

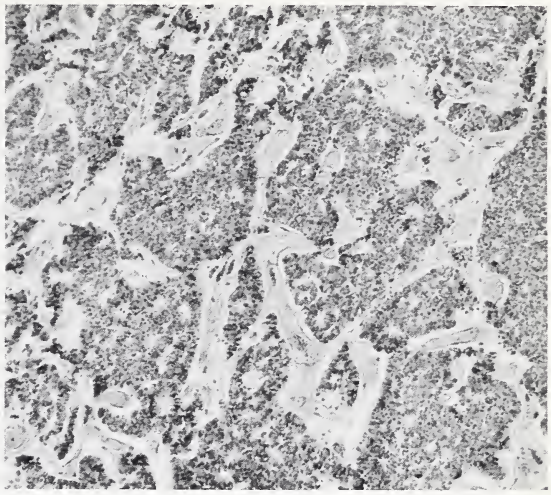


Fig. 42

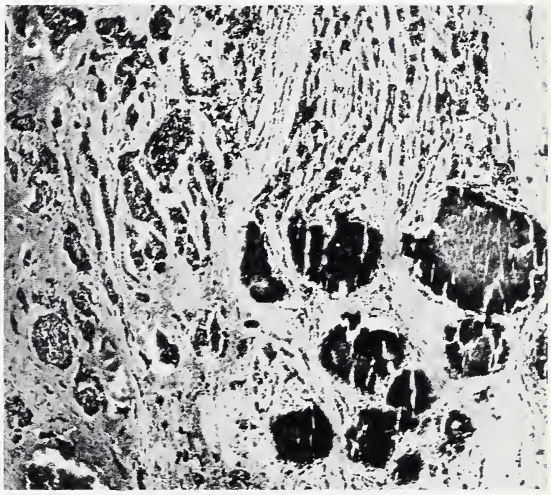


Fig. 43

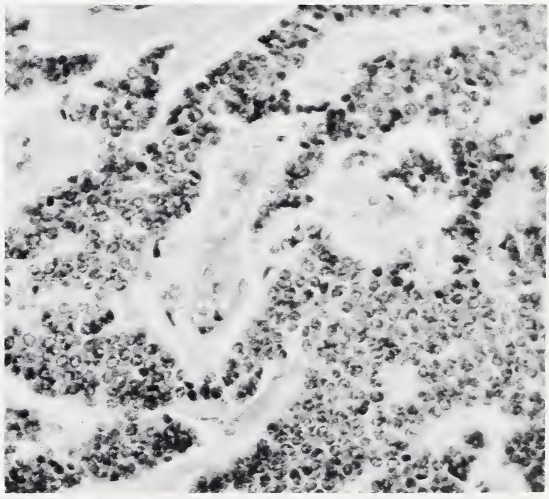


Fig. 44

CARCINOID TUMOR OF ILEUM, METASTATIC IN LUNG

(Figures 45 and 46 are from the same case)

Figure 45. Pulmonary metastasis from a carcinoid primary in the ileum. The nodule shows no relationship to the mucosa of a bronchus or a bronchiole. Compare with figures 30 and 42. × 45. A. F. I. P. Acc. No. 218737–44.

Figure 46. Detail of figure 45. Compare with figure 44. × 230. A. F. I. P. Acc. No. 218737–69.

SITE OF ATTACHMENT OF ADENOMA OF THE BRONCHUS

(Figures 47 and 48 are from the same case)

Figure 47. Residual bronchiectasis remaining three months after an obstructing adenoma, carcinoid type, was removed bronchoscopically. A. F. I. P. Acc. No. 218737–268.

Figure 48. Histologic section from the region of scarring in the common basal bronchus shown in figure 47. No tumor tissue is seen. There is squamous metaplasia of the bronchial epithelium whose supporting stroma has the structure of granulation tissue. A. F. I. P. Acc. No. 218737–113.

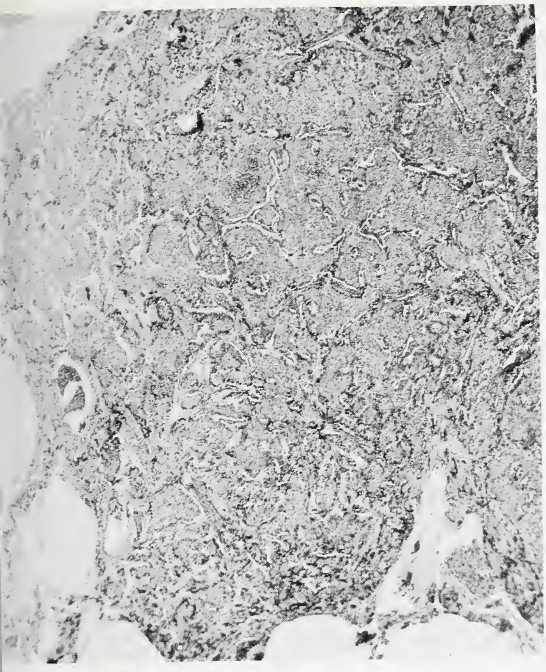


Fig. 45

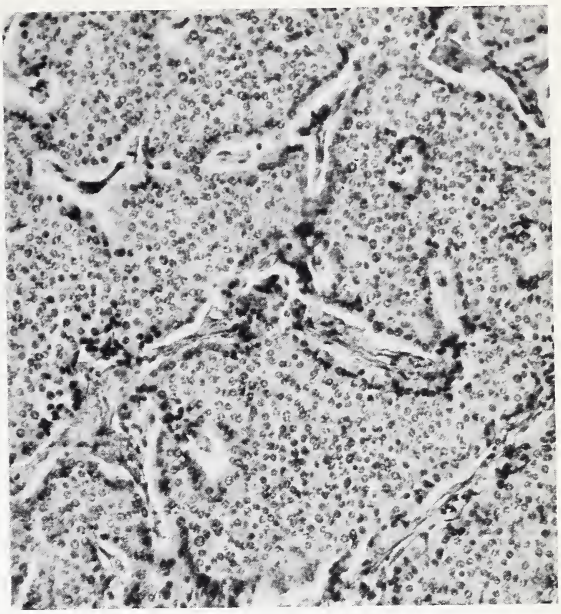


Fig. 46

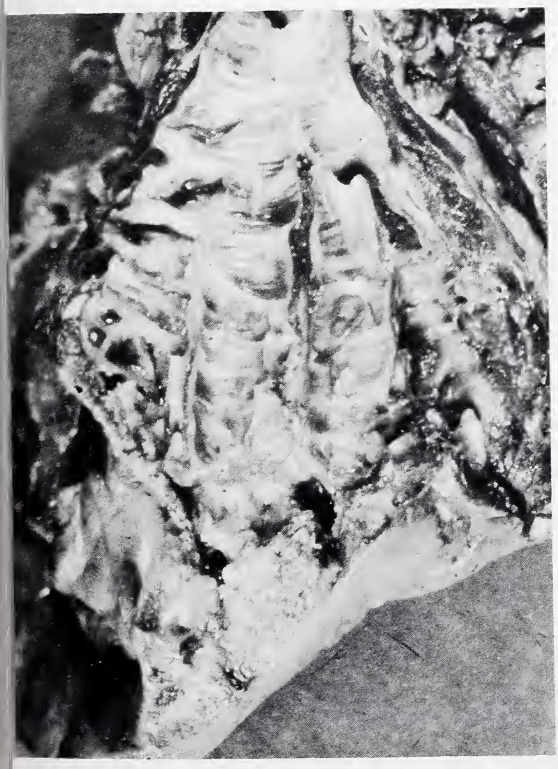


Fig. 47

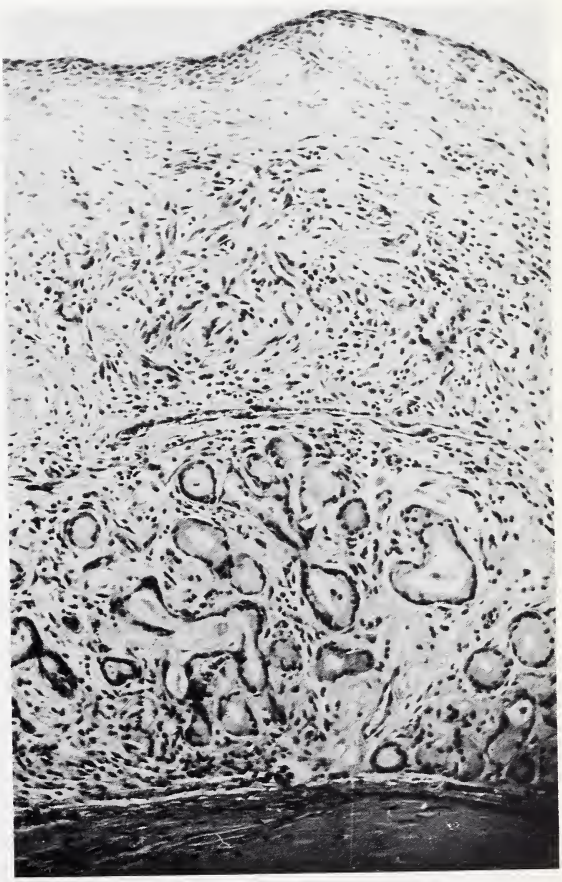


Fig. 48

ONCOCYTOID VARIANT OF CARCINOID FORM. Rarely it happens that a tumor otherwise resembling the type of bronchial adenoma that has just been described in the gross, except for a tendency toward a yellow or tan rather than pink color, is seen under the microscope to be composed in part or entirely of "oncocytes." Hamperl described these cells and found them especially in aging individuals. Although of diverse origins, these cells have at least structural if not other features in common: a large size (the term itself is derived from the Greek word meaning "increase in bulk"), a granular or striated opaque cytoplasm, and a small centrally placed nucleus that possesses a coarse network of chromatin. The oxyphilic element of the senile parathyroid is the morphologic prototype of this cell. Such cells are frequently seen in the bronchial mucous glands in the older age groups. In bronchial adenomas, they may occur in nodular masses delimited by septa of delicate connective tissue from groups of carcinoid cells (figs. 35, 36). The groups of oncocytes are closely crowded, supported by very scanty stroma, and the vascular channels are inconspicuous. In some places there is commingling with the carcinoid elements, and transitional cell forms may be found suggesting that the oncocytes are derived from the former. Bronchial adenomas composed entirely of oncocytes have been described by Hamperl (1937) and by Stout (1943). These closely resemble the oncocytoid adenomas of the salivary glands. Too few have been reported to permit an accurate clinical description.

GROSS, CYLINDROID FORM. In position the cylindroid tumors tend to be even more proximal than the carcinoid, often involving the main carina or even the trachea. In fact, these tumors comprise the most common benign tumor of the trachea; on the other hand, the carcinoid tumors are seen in the trachea with utmost rarity. It may not be possible to distinguish the cylindromatous tumors grossly from those of carcinoid structure. They may be polypoid or globoid, like the latter, but they are likely to extend more diffusely along the walls of the bronchi, whose branches may become narrowed or completely obstructed by irregular protrusions (figs. 49, 50). In such instances, there is no obvious capsule, and the extent of the intramucosal extension may be impossible to state from the gross appearance. A major bronchus may appear to be completely lined by the tissue that protrudes in irregular bosselations, and histologic sections still reveal that the integrity of the original lining epithelium has been preserved despite the apparently invasive character of the tumor (fig. 52). The cylindroid tumors in contrast to the carcinoid forms tend to be paler, firmer, and more translucent with a cut surface characteristically moist with a material suggesting thin mucus.

MICROSCOPIC, CYLINDROID FORM. The epithelial cells of the cylindroid adenomas in contrast to those of the carcinoid variety are more pleomorphic and more variable in staining quality. The cell bodies are smaller and more basophilic. The nuclei vary in size and are often fusiform. Mitoses are

more frequently observed, and may be numerous in some cases. The pattern of cell arrangement is in branching cylinders or tubes, lined often by a double layer of cells, and in plexiform honeycomb-like masses (figs. 52–55). Rarely the cell mass may resemble basal cell carcinoma of the skin and may even show central keratinization (fig. 56). The smaller acini and the interstices of the larger compound acini may be filled with an acidophilic granular material, staining with mucicarmine. This secretion, apparently produced by the epithelial cells, is an important point in differentiating this form from the carcinoid type. The stroma is a loosely arranged connective tissue much less vascular than in the carcinoid variety. There is less tendency to hemorrhage and again no tendency to necrosis except occasionally at the surface. As mentioned in the gross description, the invasive tendencies of this tumor are more pronounced, and the cartilage is not only enveloped but itself often suffers invasion (fig. 54). Extension into the septa and even into the surrounding pulmonary substance may also be observed (fig. 53).

MUCOEPIDERMOID VARIANT OF CYLINDROID FORM. A few bronchial adenomas have a histologic pattern in which there is an intimate admixture of well differentiated mucous cells and sheets of cells suggesting squamous epithelium (figs. 57, 58). Dr. Hans F. Smetana* has separated out this group of adenomas and called them "muco-epidermoid tumors" in accordance with the muco-epidermoid tumors of the salivary glands described by Stewart, Foote, and Becker. They are here classified as a variant of the cylindromas. In two cases observed at the Armed Forces Institute of Pathology, the tumors produced mucus, and the amount and character of the stroma resembles more that of the cylindroid than of the carcinoid adenomas. One of the two tumors, although well circumscribed in the gross, shows local invasion on microscopic section.

Dr. Smetana has seen several cases of bronchogenic carcinoma at the Armed Forces Institute of Pathology which he interprets as the malignant counterpart of this adenoma. The histologic appearance of one of these carcinomas is illustrated in figures 98 and 99.

TREATMENT, ADENOMAS OF THE BRONCHUS. The question of the transbronchoscopic or surgical approach has been debated many times. In an occasional instance bronchoscopic removal has been successful as subsequent microscopic inspection of the bronchus of origin may reveal no trace of tumor—only the granulation tissue to be expected after a surgical attack on the mucous membrane (figs. 47, 48). There is, however, no way of predicting how much of the lesion is actually intrabronchial and how much is encapsulated within, or actually invades, the pulmonary substance, especially when an organizing pneumonitis obscures the roentgenographic delineation of the borders of the neoplastic mass. No more than a quarter of the adenomas are exclusively

*Chief of the Division of Pathology, Armed Forces Institute of Pathology.

ADENOMA OF THE BRONCHUS, CYLINDROID TYPE

(Figures 49–55 are from the same case)

Figure 49. Cut surface of right lower lobe sectioned in a plane carried longitudinally through the intermediate and common basal bronchi. Tumor projects into the lumina of the bronchi, and extends into branch bronchi and into the surrounding lung. Bronchiectasis is present distal to the tumor in the basal segments. This is from a surgical specimen of the right lower and middle lobes transected through the intermediate bronchus. There was tumor tissue in the cut end of the intermediate bronchus, but no recurrence by X-ray two years later. A. F. I. P. Acc. No. 218737–23.

Figure 50. Detail of figure 49. The glistening, pale, translucent tumor tissue produces irregular bosselations within the common basal bronchus, but there is no ulceration of the epithelium (see figure 52). A. F. I. P. Acc. No. 218737–114.

Figure 51. Histologic section of tumor shown in figures 49 and 50. "Swiss cheese" and tubular patterns characteristic of cylindroid tumors are shown. There is hyalinization of portions of the stroma, which is much less vascular than in the carcinoid type of bronchial adenoma. × 105. A. F. I. P. Acc. No. 218737–27.

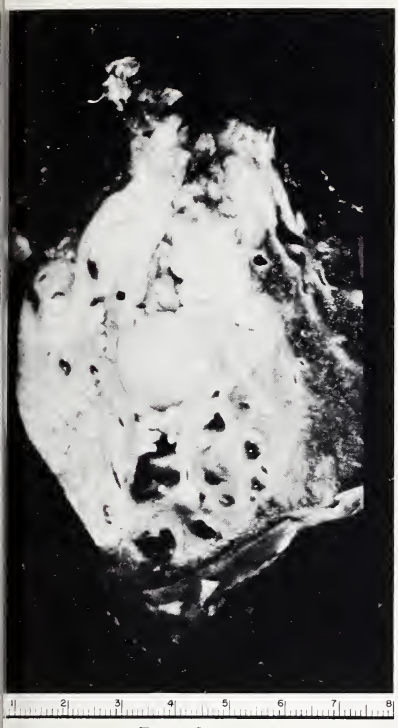


Fig. 49

Fig. 50

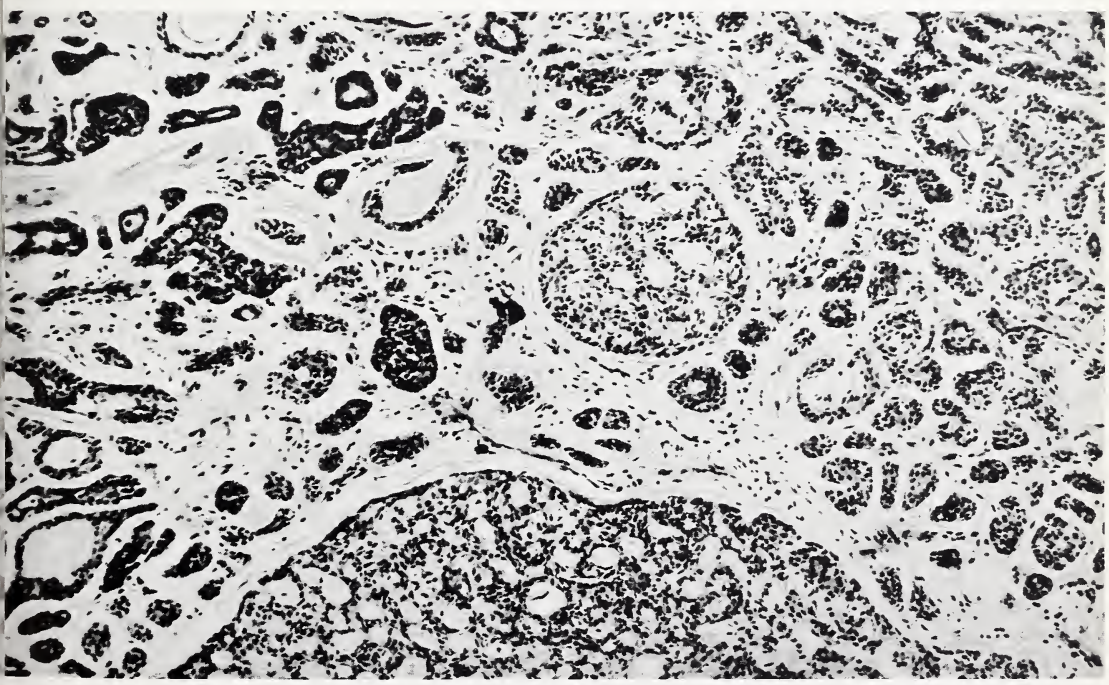


Fig. 51

ADENOMA OF THE BRONCHUS, CYLINDROID TYPE

(Figures 49–55 are from the same case)

Figure 52. Histologic section of one of the bosselations shown in figure 50. The ciliated epithelium at the surface is intact, despite the masses of neoplastic tissue in the underlying stroma. × 85. A. F. I. P. Acc. No. 218737–115.

Figure 53. Histologic section of a pulmonary septum from the specimen shown in figure 49 demonstrating invasion of the septum. × 120. A. F. I. P. Acc. No. 218737–116.

Figure 54. Histologic section of tumor shown in figure 50, illustrating invasion of the bronchial cartilage by cylindromatous epithelium. × 85. A. F. I. P. Acc. No. 218737–117.

Figure 55. Histologic section of the same tumor shown in figure 50. A mitosis can be seen just above the center of the field. × 275. A. F. I. P. Acc. No. 218737–57.

Fig. 52

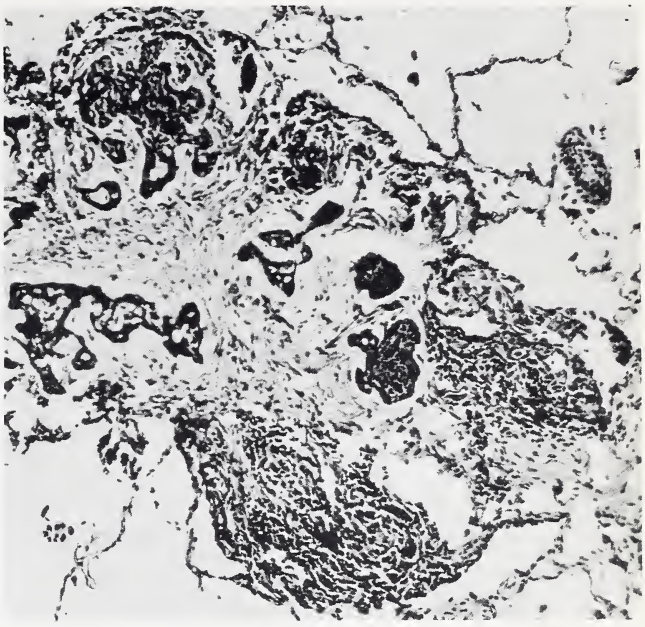


Fig. 53

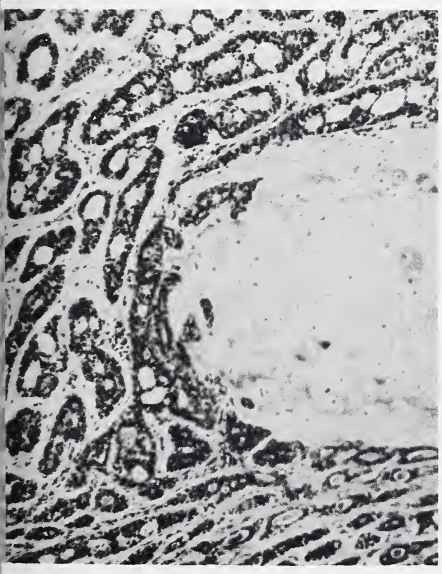


Fig. 54

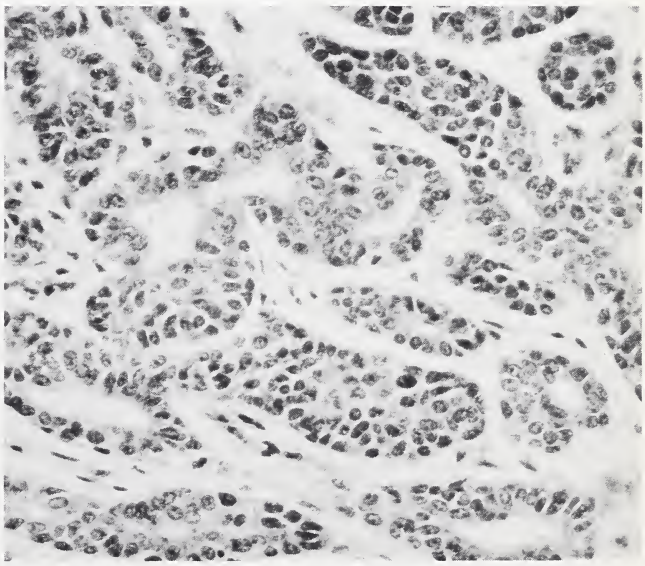


Fig. 55

ADENOMA OF THE BRONCHUS, CYLINDROID TYPE

(Figures 57 and 58 are from the same case*)

Figure 56. An unusual histologic form of adenoma of the bronchus, cylindroid type. A squamous pearl is in the center of a mass of cells resembling basal cell carcinoma of the skin. The tumor was found in the bronchus of the left lower lobe removed from a 37-year-old woman in whom an asymptomatic density in the same area had been discovered by X-ray two years previously. There was evidence of recurrence of the tumor five years after lobectomy. (This is figure 12a in Holley, S. W. Bronchial Adenomas. Mil. Surgeon, 99: 528–554, 1946.) A. F. I. P. Acc. No. 218737–272.

Figure 57. Higher magnification from an area of the tumor illustrated in figure 58. The cysts are lined by a single layer of well differentiated mucous cells surrounded by sheets of cells suggesting squamous epithelium. In other areas of the tumor the stroma is more abundant and in places hyalinized. A. F. I. P. Acc. No. 180495.

Figure 58. Mucoepidermoid variant. The bulk of the tumor projects into the lumen of the bronchus. It came from a right lung removed from a 52-year-old woman who had had a chronic productive cough of one year's duration. The adenoma projected into and obstructed the major bronchus to the lower lobe as a sessile, polypoid mass, 2 cm. in greatest dimension, and elongated along the long axis of the bronchus. The segments of the lung distal to the obstruction were bronchiectatic. The patient three years after pneumonectomy was well and showed no recurrence of symptoms. A. F. I. P. Acc. No. 180495.

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*Case contributed to the Armed Forces Institute of Pathology by Dr. Ralph H. Fuller, Tucson, Ariz.

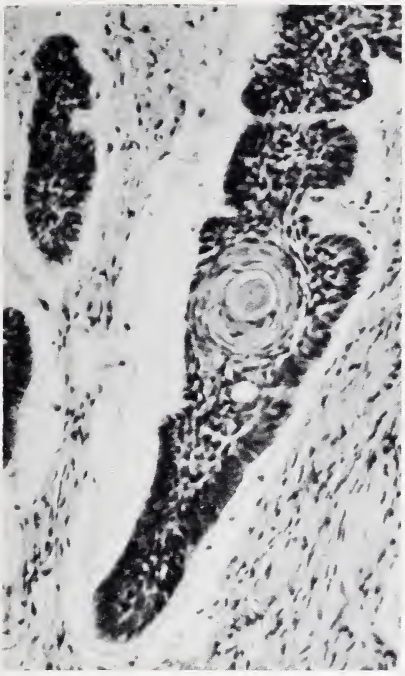

Fig. 56

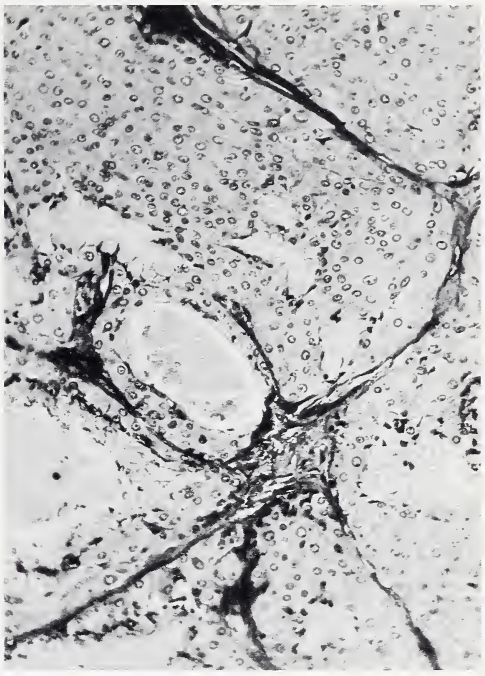

Fig. 57

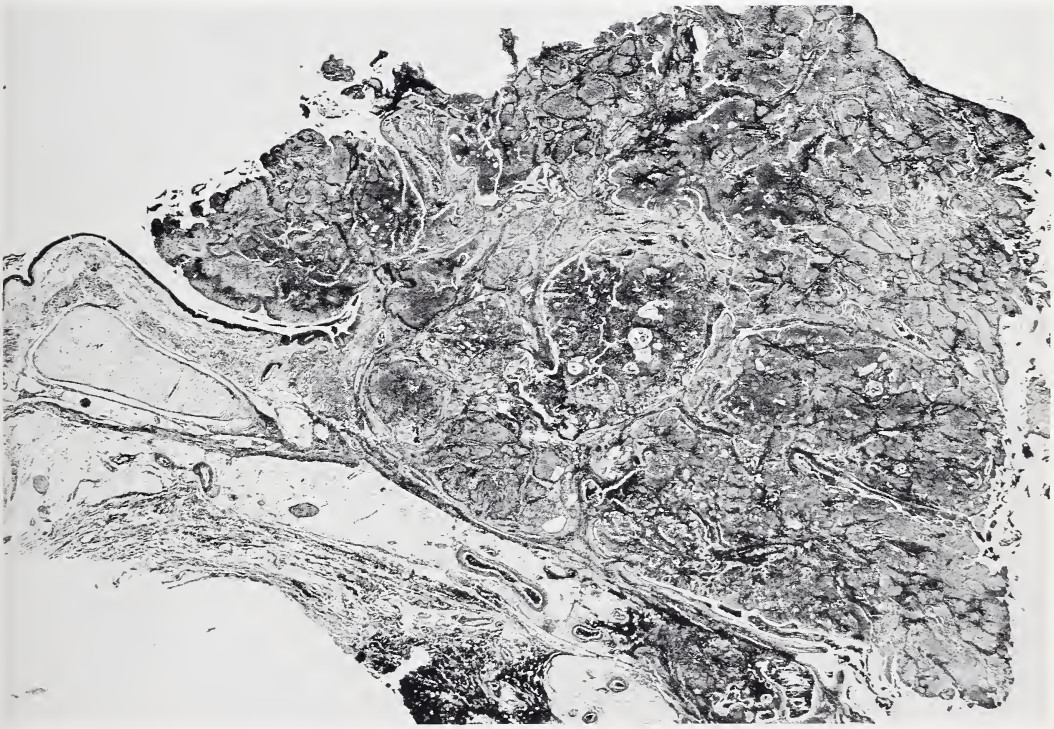

Fig. 58

intrabronchial. Furthermore, a lung the seat of organizing pneumonitis and bronchiectasis of long standing is unlikely to be restored to useful function merely by the removal of the obstructing tumor (fig. 47). The histories of patients less successfully treated transbronchoscopically indicate that local recurrence and with it recurrent disability are common. The longer the tumor is allowed to remain in situ, the greater the chance of destructive invasion or metastasis. For these reasons, and for the danger of hemorrhage already mentioned, the better treatment appears to be lobectomy, bilobectomy, or pneumonectomy as indicated by the conditions of the case.

Carcinoid tumors are notably radio-resistant, although some have described an inhibition of development after such therapy. The cylindromatous tumors, on the other hand, may show marked regression after X-ray therapy.

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Bronchiolar Carcinoma

SYNONYMS AND RELATED TERMS: "Carcinoma bronchiolorum" (Lat.); adenomatosis; adenoma-like tumor of lung; alveolar carcinoma; alveolar cell cancer; alveolar cell carcinoma; alveolar cell tumor of lung; "benign alveolar cell tumor of lung"; cancerous pulmonary adenomatosis; carcinoma of alveolar epithelium; carcinomatoides alveogenica multicentrica; carcinosis; diffuse alveolar cancer; diffuse bronchiolar carcinoma; "diffuse circumscribed bronchiolar carcinoma"; diffuse epithelial hyperplasia; diffuse lung carcinoma; "diffuse primary alveolar carcinoma"; "diffuse primary alveolar epithelial carcinoma"; epithelialization of alveolar walls; malignant adenomatosis; mucocellular papillary adenocarcinoma; multicentric alveolar cell carcinoma; "multiple bronchiolar carcinoma"; "multiple circumscribed bronchiolar carcinoma"; multiple nodular carcinoma; "multiple pulmonary adenomatosis"; papillary gelatinous adenocarcinoma; "primary multiple alveolar cell tumor"; primary multiple carcinoma; pulmonary adenomatosis, benign; pulmonary adenomatosis, malignant; pulmonary alveolar adenomatosis; pulmonary mucous epithelial hyperplasia; "solitary bronchiolar carcinoma"; terminal bronchiolar carcinoma.

Under bronchiolar carcinomas shall be included diffuse or focally distributed acinar tumors supported mainly upon the walls of the alveoli, usually bilateral, but slow to metastasize beyond the lung. The peripheral position, probable multicentric origin, relatively benign histologic appearance of many of these lesions, and the frequent failure to metastasize, despite massive involvement of both lungs, set them apart from the bronchogenic carcinomas.

A histologically benign variant often referred to as pulmonary adenomatosis has been considered as an entity different from bronchiolar carcinoma. However, transitional forms have been shown to exist, and there are no reliable histologic criteria that serve to distinguish tumors that are localized to the lung from those that have metastasized. These tumors usually produce death by their local effects on the pulmonary parenchyma rather than by metastases.

Two schools of thought exist concerning the histogenesis of this lesion. One maintains that alveolar cells and the other that bronchiolar lining cells are the source of the tumor. Some idea of the divergence of opinion concerning the very existence of alveolar lining epithelium may be gathered from a perusal of Macklin's report of a symposium on the subject. There is no disagreement that in disease the interalveolar septa may very rapidly acquire an investment of tall lining cells, but whether these cells are endodermal (derived from the neighboring bronchi) or from mesodermal elements (e. g., septal cells) is again in dispute. That this distinction may be somewhat fatuous is brought out by

Waddell's cytologic and histochemic observations, which suggest that the epithelium of the bronchioles is itself of mesodermal origin. There is no doubt that cells of mesodermal origin can give rise to tumors with an adenocarcinomatous structure, witness certain of the synovial tumors of large joints. Thus, there is no theoretical reason why alveolar lining cells of whatever origin cannot give rise to an adenomatous or adenocarcinomatous lesion. Scrutiny of these lesions under the low power of the microscope, however, reveals not only a geographic association with the terminal bronchioles, but also replacement of portions of their lining epithelium by the neoplastic cells (fig. 63). Such observations support the theory of the bronchiolar origin of these tumors. The discontinuous alveolar investment cited by some as evidence that alveolar cells are the source of these tumors may be more apparent than real. There exists also the mechanism of implantation of aspirated neoplastic epithelium upon the supporting stroma of the alveoli. This has been demonstrated experimentally by Furth, and occurs occasionally in metastatic tumors. This aspirative phenomenon plays a role in the intrapulmonary dissemination even of primary bronchogenic carcinoma (fig. 87), the so-called "cancerous pneumonia." Thus the alveoli in the bronchiolar carcinoma may become covered by tumor cells either by continuous downgrowth from the bronchioles or by aspiration. In this way, primary lobules become involved.

The rarity of involvement of the intrapulmonary lymphatics suggests that the lesion is multicentric in origin.* Isolated atypical proliferations involving bronchioles may have a striking resemblance to the diffuse bronchiolar carcinoma (figs. 9–11).

The similarity of bronchiolar carcinoma in man, especially in its histologically more benign and diffuse form, to a contagious disease of sheep known as jaagsiekte, and to a similar condition in goats and guinea pigs, has been noted by many observers. A few distinguishing histologic minutiae have been described, but these are altogether within the limits of variation in the human disease. The sluggish contagiousness of the ovine disease has been described by Dungal. In at least one instance, a woman had been in contact with sheep (in Montana) which were suffering from the ovine form. A few alert observers have attempted, without success, the transmission of the disease of man to animals including sheep, monkeys, guinea pigs, and rabbits. It is interesting to note that even in sheep, metastases may occur (Aynaud quoted by Paul and Ritchie).

There are some microscopic similarities also to the multiple tumors of mice, either spontaneous or induced with carcinogenic agents.

In patients the only suggestive factor is the association with organizing pneumonitis in some instances. Whether this pneumonitis has a specific etiology and whether it precedes or is consequent upon the neoplastic process requires further observation and study.

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*See footnote, p. 62.

NATURAL HISTORY. Bronchiolar carcinoma comprises between three and four percent of the malignant tumors of the lung. Men and women are affected about equally. The age distribution is wide, patients from 17 to 89 years old having been reported. As reports have accumulated, it would seem that most cases occur in patients between the ages of 50 and 59, although in earlier reports patients were predominantly younger than 50.

Since there is no ulceration or obstruction of major bronchi and thus no atelectasis or obstructive pneumonitis, these tumors have a more insidious onset than the bronchogenic carcinomas. They also differ in several other important respects. An asymptomatic case detected by routine roentgenography has been reported by Swan. In most of the patients reported by him, the symptoms were from 4 to 15 months' duration, and it is probable that the lesion is already of some duration when first manifest clinically. When symptoms have developed, the course leading to ultimate fatality is brief. Exceptions exist as reported by Delarue and Graham (6 years) and Paul and Ritchie (probably 7 years). Cough is less common than in bronchogenic carcinoma, and sputum is rarely sanguineous, although exceptions have been reported. Usually it is watery or mucoid and may reach a daily output as great as 1800 cc. In many instances, the first symptom is that of dyspnea. This may be associated with cyanosis. Both result from the fact that massive amounts of parenchyma of both lungs are ultimately involved. Clubbing of the fingers may occur, and there may even be evidence of cor pulmonale in some instances. These symptoms usually exist without evidence of acute infection, but some individuals may have fever, night sweats, and loss of weight. In an occasional instance there may be evidence of distant metastases.

The roentgenographic changes suggest an organizing pneumonitis in the more diffuse forms (fig. 59) or disseminated metastatic carcinomatous lesions in the nodular form. Taken in conjunction with the history and findings as they have been outlined, the diagnosis may be suggested. Hatfield and Hill have described the finding of a number of small circumscribed round or oval masses of epithelial cells with a strikingly regular ovoid outline in repeated samples of sputum as being suggestive of the condition. These, however, may be seen in bronchogenic adenocarcinoma (fig. 141).

GROSS. Two main forms have been distinguished on the basis of the gross distribution of the lesions—a diffuse and a nodular variety; combination forms also occur. The diffuse or combined forms account for approximately two thirds of the cases.

The diffuse form involves a considerable portion of the parenchyma and merges gradually into typical pulmonary substance (fig. 60). It has been variously described as resembling lobar pneumonia in the stage of grey hepatization, organizing pneumonia, or lipoid pneumonia. Generally, the cut surface is soft and yellow-white or grey-pink and characteristically exudes gelatinous or mucoid material in abundance. Necrosis in this variety is not in

BRONCHIOLAR CARCINOMA

(Figures 59–63 are from the same case)

Figure 59. Roentgenogram taken June 20, 1940 just before left pneumonectomy. The extensive poorly delimited shadow in the left lung field suggests organizing pneumonitis. Smaller shadows can be seen in the right lung field. A. F. I. P. Acc. No. 218737–118.

Figure 60. Section of specimen shown in figure 61. The general appearance is suggestive of organizing pneumonitis, although the tissue is somewhat more translucent and exudes considerable mucoid material. In the upper lobe, the tissue is firmer and contains variable cystic spaces lined with glistening membranes and filled with clear mucus. This is an unusual feature of bronchiolar carcinoma. A. F. I. P. Acc. No. 218737–121.

Figure 61. Left lung removed from patient whose roentgenogram taken just before the operation is shown in figure 59. The visceral pleura is thickened but was not adherent to the parietal pleura, although the interlobar fissure is obliterated. The underlying parenchyma is indurated. A. F. I. P. Acc. No. 218737–120.

Fig. 59

Fig. 60

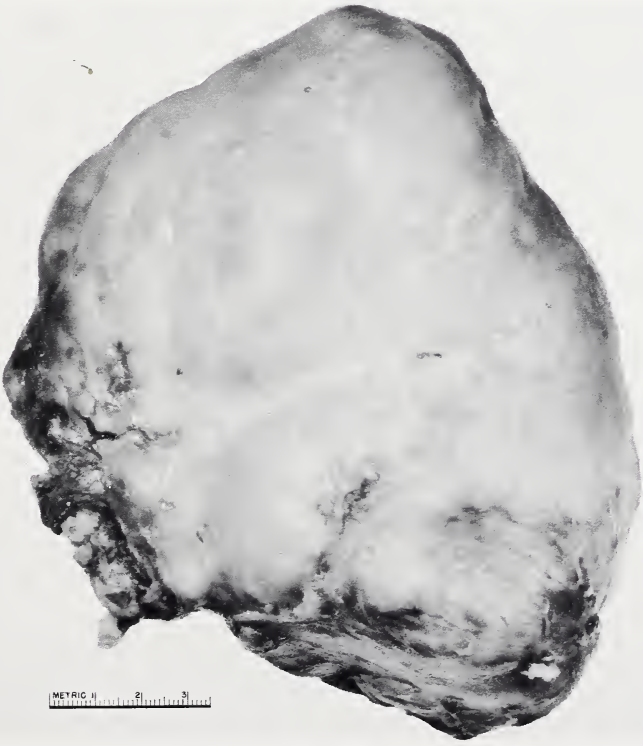

Fig. 61

evidence grossly, although there may be an accompanying necrotizing and organizing pneumonitis. Occasionally, minute cystic spaces may be formed (figs. 60, 62). The nodular disseminated form (fig. 64) has been described as resembling noncaseating miliary tuberculosis in some instances. Usually the nodules are larger, resemble metastatic carcinoma, and may show evidence of necrosis and umbilication. A primary origin elsewhere must be excluded with extreme care.

The pleura overlying the lesions is thickened (fig. 61), and there may be nodules immediately beneath it in the disseminated form. According to Swan, fibrous adhesions usually partially or completely obliterate the pleural space when the disease is responsible for the death of the patient. At least 80 percent of the cases are bilateral when first seen, or there is soon evidence of spread to the other lung.

MICROSCOPIC. The characteristic cell type is a tall columnar cell with finely granular cytoplasm, somewhat resembling that of the bronchial epithelium (fig. 63). The cytoplasm is more abundant and more palely staining. The nucleus also is more vesicular, rounder, and larger than that of the bronchial cell but still relatively small in comparison with the cytoplasmic mass. There are several small but prominent nucleoli. These cells may occur in a single layer, but at times are multilayered or may occur in solid masses. In some instances the cells may become quite bizarre, with basophilic cytoplasm and irregular or even multiple nuclei that project variably into the lumina of the acini. Mitotic figures generally are rare, but are relatively common in these more atypical cells. Such cells may occur together with those of less malignant appearance. Especially in the disseminated form, the epithelium may resemble more closely that of the bronchioles. Cilia are rarely present (fig. 66). These tumors usually produce mucus, often in abundance, as do the cells of any pulmonary adenocarcinoma. In the mucus-producing epithelium the nuclei are basally placed. Much of this epithelium appears to be supported by the interalveolar septa. These may be thin, but in some instances are thickened by edema, granulation tissue, and cellular exudate of an organizing pneumonitis that may accompany the process. This pneumonitis may involve the parenchyma that intervenes among foci of the atypical epithelial cells. In the disseminated form, atypical cells may occur at the margins of such lesions (fig. 65). The pneumonia may cause death before metastases occur.

Careful study will demonstrate that patches of atypical epithelium may abut directly on that lining normal bronchioles (fig. 63), and inspection under low power of the margins even of diffuse lesions will reveal that the tumor cells are localized about bronchioles (fig. 62), suggesting that the columnar or cuboidal epithelial cells of these structures are the source of the neoplastic tissue which then grows out upon the supporting interalveolar septa.

In exceptional instances, interalveolar septa may be broken down as the proliferative process continues, and large spaces are formed which are lined

BRONCHIOLAR CARCINOMA

(Figures 59–63 are from the same case)

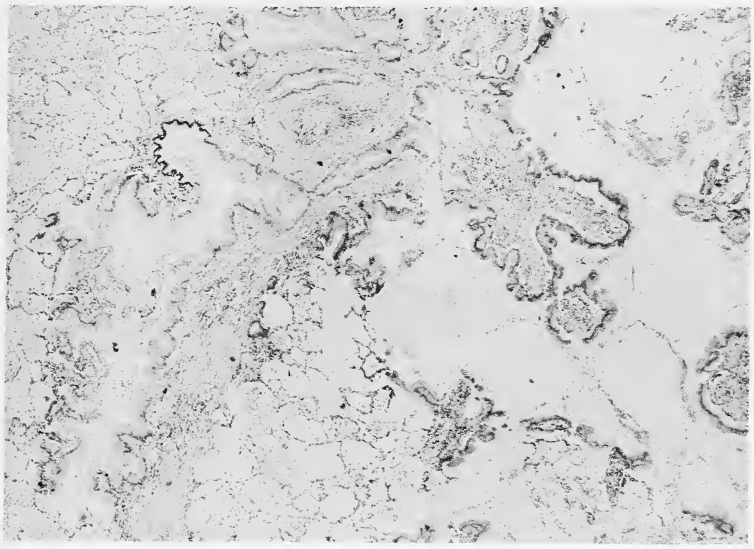

Fig. 62

Figure 62. General view of tumor shown in figures 60 and 61. A bronchiole lined by typical ciliated epithelium opens into a ramifying series of spaces lined by nonciliated atypical mucus-producing epithelium. The latter is supported on the thickened walls of the more distal respiratory passage, or on thin interalveolar septa. The low power view provides the proper orientation for considering the origin of the tumor and its mode of spread. Compare with figure 9. × 31. A. F. I. P. Acc. No. 218737–66.

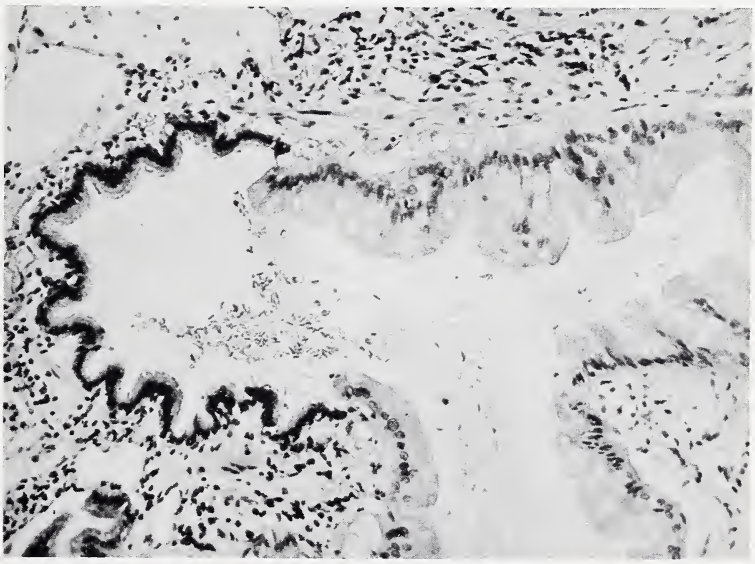

Fig. 63

Figure 63. Detail of figure 62 showing the bronchiole at the junction of the ciliated psudostratified and the atypical epithelium. The cells of the latter have vacuolated cytoplasm and ovoid nuclei, Note resemblance to the "atypical proliferation" shown in figures 10 and 11. × 170. A. F. I. P. Acc. No. 218737–122.

BRONCHIOLAR CARCINOMA

(Figures 65–67 are from the same case)

Figure 64. Close-up of a gross specimen of the focal disseminated form of bronchiolar carcinoma. (This is figure 1 in Swan, L. L., Pulmonary adenomatosis of man. A review of the literature and a report of nine cases. Arch. Path., 47: 517–544, 1949. From the Armed Forces Institute of Pathology.) A. F. I. P. Acc. No. 58048.

Figure 65. Histologic section of a nodule from another instance of focal disseminated bronchiolar carcinoma. The lesions grossly resembled foci of organizing pneumonitis. The nodule consists of dense connective tissue supporting long branching acini most numerous at its margin. Near the lower margin of the nodule atypical epithelium appears to line and infiltrate the walls of two bronchioles. × 20. A. F. I. P. Acc. No. 218737–62.

Figure 66. Detail of figure 65. Irregular acini are lined with ciliated epithelium. × 220. A. F. I. P. Acc. No. 218737–125.

Figure 67. Detail of figure 65. Tumor cells within lymphatics compress a blood vessel. × 160. A. F. I. P. Acc. No. 218737–126.

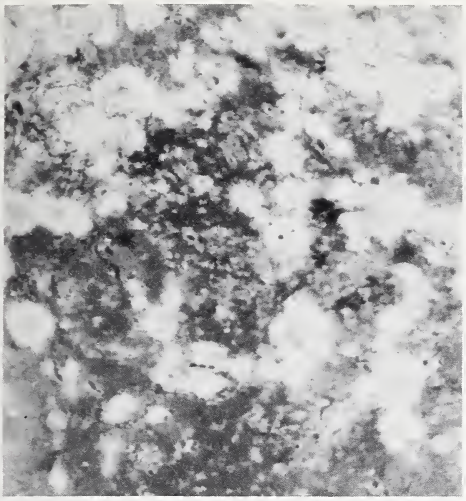

Fig. 64

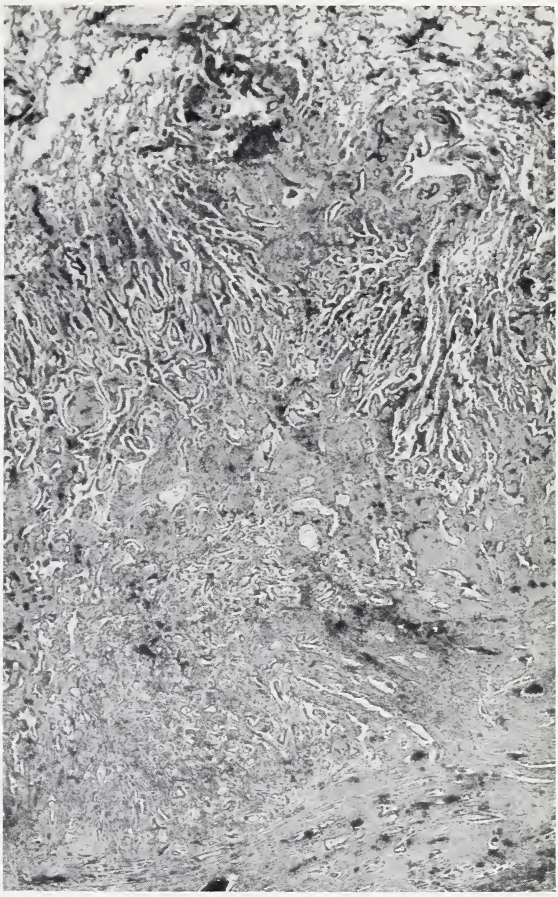

Fig. 65

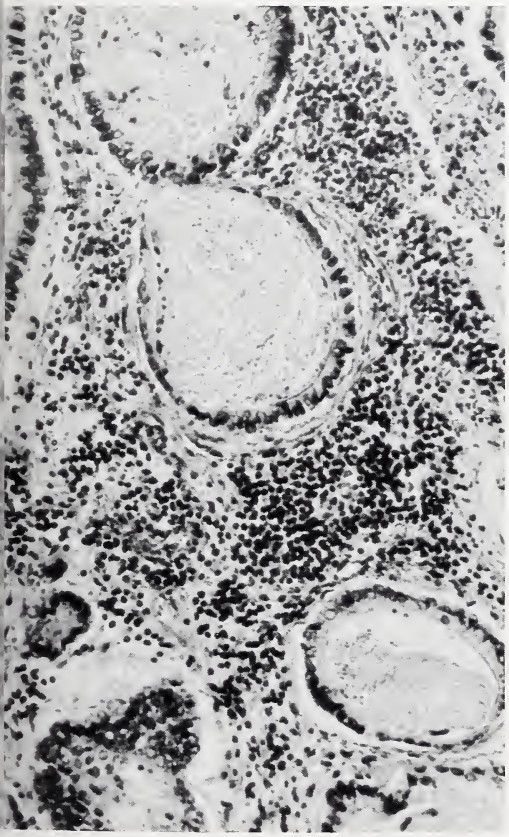

Fig. 66

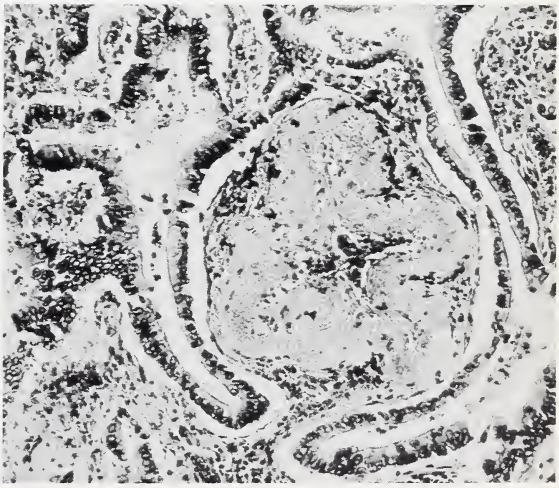

Fig. 67

by the atypical epithelium. Thus the tissue grossly may acquire a spongy "emphysematous" appearance (figs. 60, 62).

Intrapulmonic lymphatic spread may be observed, but is not common, and it would appear that the lesion is truly multicentric in origin. In the focal disseminated variety, evidence of lymphatic spread may be more prominent (fig. 67; also fig. 4 in Swan).

METASTASES are evident in more than one half of the patients. In 50 percent of these patients only bronchial or tracheal lymph nodes are involved. In the others, there are distant metastases. Then the brain alone may be involved, or else the metastases may be widespread with involvement also usually of the liver, remote lymph nodes, kidneys, adrenals, and pericardium.

TREATMENT. Both prognosis and treatment are affected by the fact that the condition tends ultimately to involve both lungs.* The insidious onset and widespread nature of the lesions make surgical treatment generally ineffective, although Delarue and Graham report a patient who was symptom free four years after lobectomy. Apparently only the right lung was involved. The disease had been present two years before lobectomy.

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*Dr. Fred Stewart, New York City, states that in his experience these tumors when operable have given the best 5-year salvage of any of the lung carcinomas (Smith, R. R., Knudtson, K. P., and Watson, W. L. Terminal bronchiolar or "alveolar cell" cancer of the lung. A report of twenty cases. Cancer, 2:972–990, 1949). Dr. Stewart therefore questions the apparent multiple origin of bronchiolar carcinoma and suggests that the multiple foci are due rather to lymphatic spread of tumor from a single focus with subsequent lining of lung acini.

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Bronchogenic Carcinoma

SYNONYMS AND RELATED TERMS: Bronchial carcinoma; bronchiogenic carcinoma; carcinoma of the lung.

In this group are discussed the tumors that appear beyond peradventure to originate in the bronchi themselves. Bronchiolar carcinoma has been discussed separately for reasons presented in the preceding section.

In most instances, especially in the squamous or anaplastic neoplasms, the surface epithelium seems to be the source of the tumor cells. Gradual transitions from atypical squamous epithelium (fig. 68), presumably metaplastic from the normal columnar lining cells, to epithelium with the appearance of "carcinoma in situ" (fig. 69), to obvious carcinoma may be observed. Rarely there are histologic features that suggest an origin in the mucous glands. Since there is evidence that mucous glands are the tissue of origin of the bronchial adenomas, the possibility that marked anaplasia may occur in such neoplasms must be considered (figs. 91–99).

It is now generally admitted, with a few dissenting voices (see Fried, Peery), that carcinoma of the lung has been increasing in incidence. This increase is above that to be expected from the aging of the population or from increasing diagnostic accuracy. Thus Rosahn in a study based on records at Boston City Hospital found that cancer of the lung in 1928 to 1937 accounted for 11 percent of all deaths from malignant disease. In the same series, there was a 49 percent increase in this decade as compared with the preceding 10 years. It is now second on the cancer mortality list in men and fifth in women.

ETIOLOGY. Consideration of etiologic factors is of high importance, since therein lies hope of prevention. The increase in incidence suggests the appearance of new factors in the modern environment. Occupational cancer of the lung has been known for many years. In 1879, the pulmonary disease known to have existed since the sixteenth century among the cobalt miners of Schneeberg, Germany, was diagnosed as sarcoma; later (1922), the diagnosis was revised to carcinoma. The disease accounted for the death of some 80 percent of the miners. The specific factors responsible for the pulmonary

Figure 68. Atypical metaplastic epithelium lining the bronchus of origin of an epidermoid carcinoma. A. F. I. P. Acc. No. 218737–140.

Figure 69. A plug of atypical epithelium near the mouth of a mucous gland, the appearance of which is compatible with "carcinoma in situ." A. F. I. P. Acc. No. 218737–141.

Figure 70. Asbestosis bodies within a carcinoma of the lung. A. F. I. P Acc. No. 218737–142.

Figure 71. A blood vessel compressed within the stroma of an epidermoid carcinoma of the lung and occluded by a recanalized thrombus. Verhoeff elastic stain. A. F. I. P. Acc. No. 218737–36.

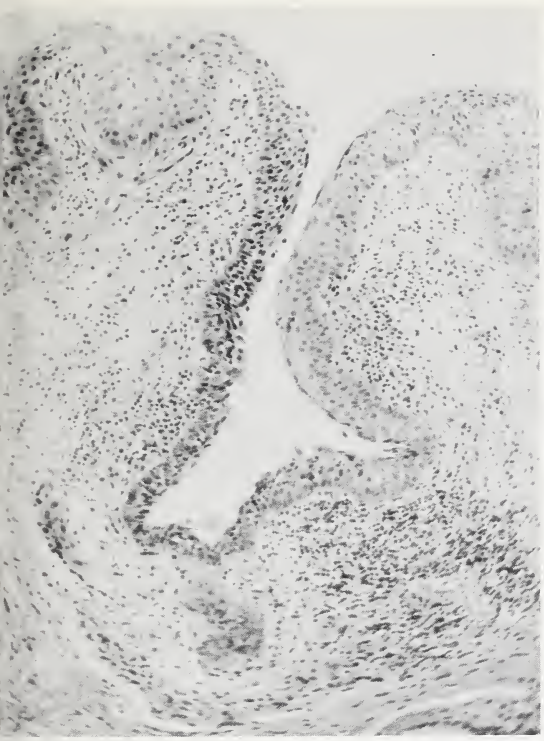

Fig. 68

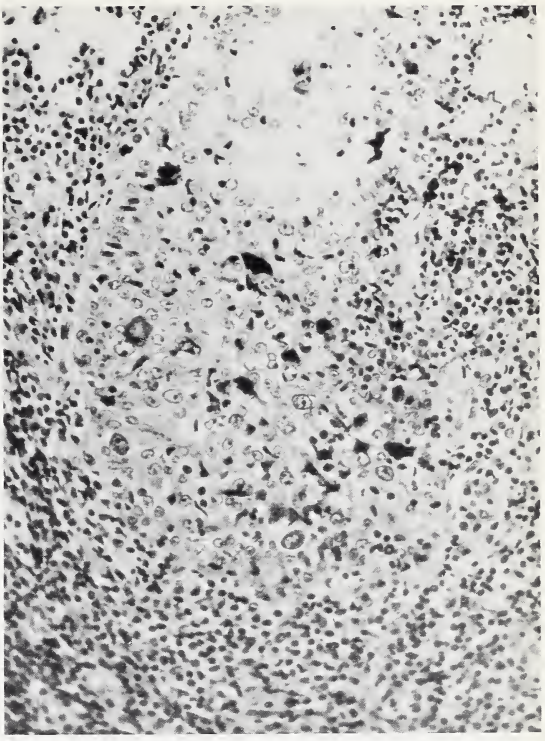

Fig. 69

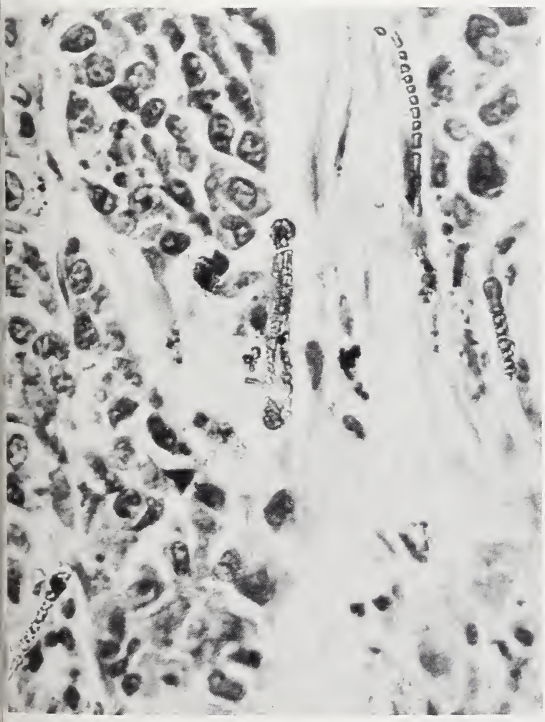

Fig. 70

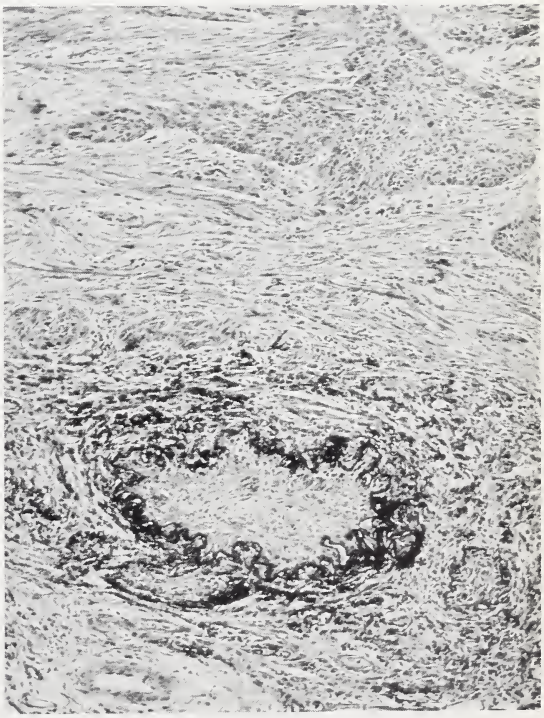

Fig. 71

carcinoma are not clear, since arsenic and uranium are also contained in the cobalt-bearing ores. Likewise, some 50 percent of the miners at the nearby Joachimstal uranium mines have died of cancer of the lung.

Arsenic has been implicated not only in tumors of the skin but also in carcinoma of the lung among workers producing a sheepdip powder (Perry, Bowler, et al.). The arsenic problem needs further investigation, especially because of the widespread use of this material in insecticides.

German reports concerning chromium as another carcinogenic agent have been confirmed in this country by Machle and Gregorius. No less than 21.8 percent of 143 deaths in seven chromium plants were from carcinoma of the lung. In this group lung tumors comprise two thirds of all the malignant neoplasms, which in themselves were in remarkably high incidence (66 of 143).

There have been a number of confirming reports (Holleb and Angrist; Hueper) of the high incidence of carcinoma of the lung in patients with asbestosis, since the first report by Lynch and Smith in 1935, but the total number of cases reported is still small for statistical significance. The asbestosis bodies may actually be found within the tumor (fig. 70). Other pneumoconioses are not known to exhibit an association with malignant disease of the lungs.

The automobile and the tarred roads associated with its use have been suspected but not definitely implicated.

The concurrent increased use of tobacco in the form of cigarettes and increased incidence of carcinoma of the lung have stimulated numerous investigations attempting to determine what possible role heavy and prolonged use of tobacco might be playing in the etiology of pulmonary cancer. This has proved to be an exceedingly difficult problem to solve. Most of the reports in the literature claiming to show significant correlation between the habit and the disease are based on series of patients including individuals without histologic proof of the diagnosis of carcinoma, or are inadequately controlled geographically, or in regard to numerous other potential etiologic factors of the modern environment. Carefully controlled experiments show that tobacco smoke is not a carcinogenic agent in mice and that tar from tobacco smoke is only weakly carcinogenic when painted on the skin of rabbits.

The atypical proliferation associated with the postinfluenzal pneumonia was early thought to be a factor predisposing to neoplasia in the lung. It has been pointed out that although Iceland suffered very heavily from influenza, there has been no disproportionate increase in cancer of the lung reported in that country. Tuberculosis is rather frequently associated with carcinoma of the lung (10.6 percent of Fried's 319 patients with carcinoma of the lung also had tuberculosis). Carcinomas sometimes arise from the walls of tuberculous cavities (pl. II–A). The etiologic connection, however, is not clearly defined.

Commercial lead (Black, 1943) and paraffinomas from mineral oil ingested for constipation (Sante, 1949) have been suggested as possible etiologic factors in the development of carcinoma of lung, but there are insufficient data for the determination of the validity of either thesis.

NATURAL HISTORY. The disease is much more frequent in men. Most observers now find the predominance in the male to be between five and ten to one. It is interesting to note that adenocarcinoma is approximately five times more frequent in women where it accounts for between 25 and 32 percent of all cases of carcinoma of the lung. Women tend to have cancer of the lung at an earlier age than men. Evidence is accumulating that the incidence of carcinoma of the lung is lower in the Negro than in the white man (Moritz).

The peak incidence is between 50 and 59 years (34 percent), but a considerable percentage occurs in the decade before and after.

The initial symptom varies, and in order of frequency, according to Lindskog and Bloomer, is cough (60 percent), hemoptysis (9 percent), dyspnea (8 percent), "pneumonia," wheezing, hoarseness, persistent moderate fever, shoulder pain, abdominal mass, or headache. When the patient seeks medical advice there is usually a combination of symptoms and signs. Uncommon chief complaints are masses in the skin, neurologic signs indicating metastases to or pressure upon the nervous system, collapse of vertebrae, and the syndrome produced by tumors at the thoracic inlet (see below). It is most unusual not to be able to demonstrate in the roentgen film a carcinoma of the lung that is producing symptoms. Asymptomatic tumors are discovered in routine roentgenographic examinations (fig. 91). The proper diagnosis and treatment of bronchogenic carcinoma at this stage offer the patient the greatest chance of cure. Evidence is accumulating that especially the well differentiated epidermoid carcinomas may exist silently for many years before symptoms appear. Late diagnoses result from failure to consider the possibility of the disease and delay in radiography, bronchoscopy, and cytologic examination of the sputum. Roentgenographic examination of the chest contributes much to the diagnosis. Highly suggestive are wedge-shaped shadows based upon the pleura, indicating bronchial obstruction with atelectasis or organizing pneumonitis. Even earlier evidence of an obstructive lesion may be localized emphysema or a localized failure of the lung to empty during exhalation. Clinically, breath sounds are diminished over such a zone while resonance is maintained. Rounded hilar shadows especially when there is evidence of enlargement of the lymph nodes are obviously suspicious. Cavitation may be confusing in that it may suggest abscess or tuberculosis. A location of the cavity close to the hilum, especially in a part of the lung where true abscess is rare, irregularity in the wall, and absence of other historical or laboratory features indicating abscess or tuberculosis are indicative of carcinoma (fig. 79). Most difficult of diagnosis is the tumor lost in more generalized consolidation; it is then that the accessory diagnostic techniques such as bronchography or section roentgenography are most helpful.

The course of bronchogenic carcinoma is very variable, some cases persisting for at least seven years and others galloping to a fatal issue within a few months after the appearance of the first symptoms.

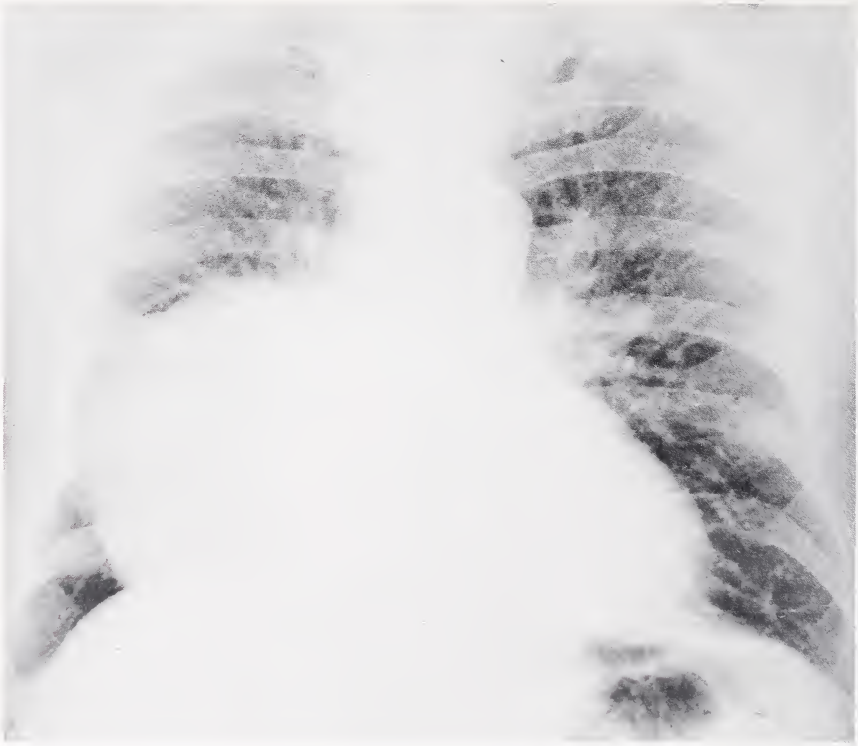

Fig. 72

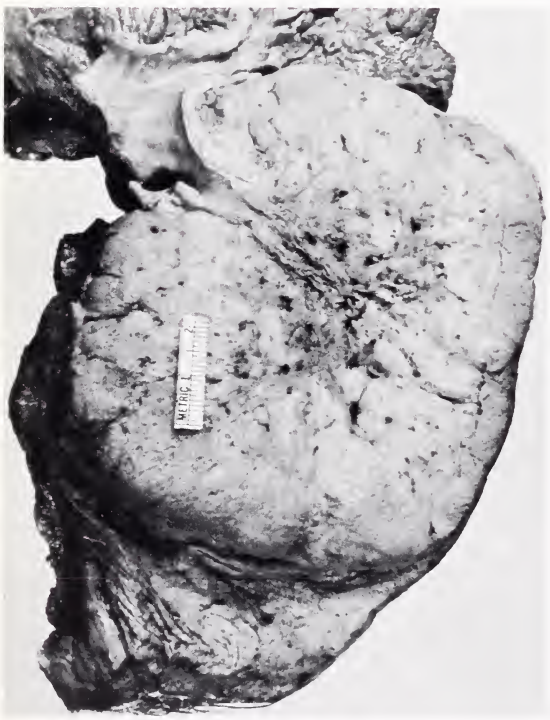

Fig. 73

Fig. 74

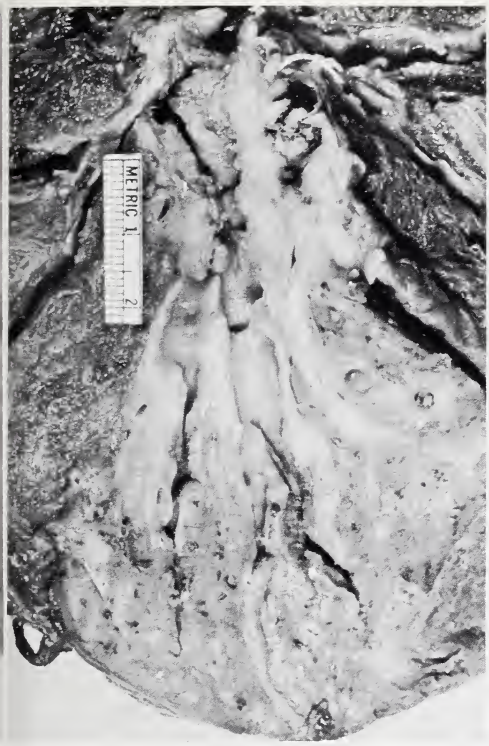

Fig. 75

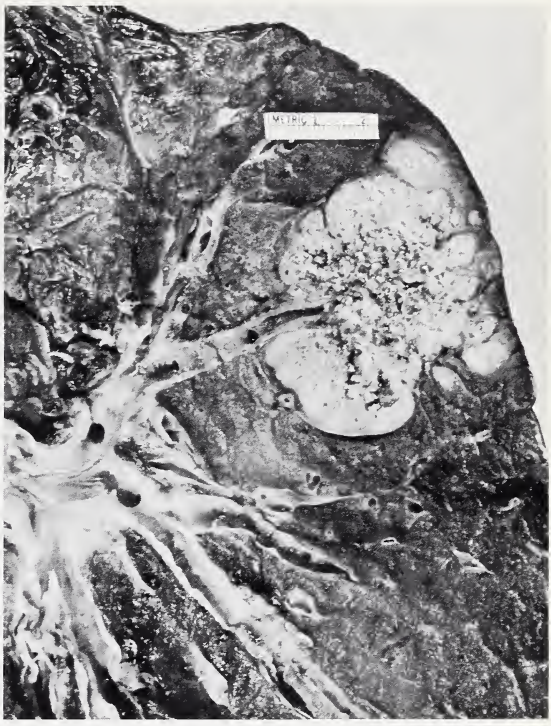

Fig. 76

BRONCHOGENIC CARCINOMA

(Figures 72 and 73 are from the same case)

Figure 72. Epidermoid carcinoma. Roentgenogram of the thorax shows a large mass with a smooth well defined margin in the right lung. A right pneumonectomy was done shortly after this film was taken. The resected lung is shown in figure 73. A. F. I. P. Acc. No. 218737–127.

Figure 73. Epidermoid carcinoma. The cut surface of the right lung (roentgenogram shown in figure 72) sectioned through the tumor mass. The tumor appears to be centered about the superior bronchus of the right lower lobe but the ulceration of distal bronchi suggests a more peripheral origin. A. F. I. P. Acc. No. 218737–128.

Figure 74. Another epidermoid carcinoma infiltrating longitudinally along a bronchus. The adjacent bronchial lymph node is invaded by direct continuity. A. F. I. P. Acc. No. 218737–129.

Figure 75. Infiltrating epidermoid carcinoma restricting lumen of common basal bronchus. Organizing pneumonitis and bronchiectasis are present beyond the obstruction. A. F. I. P. Acc. No. 218737–132.

Figure 76. A peripheral epidermoid carcinoma centered about a branch of the apical bronchus to the left upper lobe showing focal necrosis with early cavitation. A. F. I. P. Acc. No. 218737–139.

BRONCHOGENIC CARCINOMA

(Figures 79 and 80 are from the same case)

Figure 77. A massive epidermoid carcinoma with beginning central cavitation has expanded into and largely replaced the lower lobe of the left lung. The neoplasm has infiltrated longitudinally within the main lower lobe bronchus, and invaded and partially obstructed the branch of the pulmonary artery to the lower lobe. A. F. I. P. Acc. No. 218737–133.

Figure 78. Formation of a large cavity within an epidermoid carcinoma that also infiltrates proximally along the lingular bronchus. All parts of the cavity are lined by tumor. A. F. I. P. Acc. No. 218737–134.

Figure 79. Epidermoid carcinoma with cavitation. Roentgenogram showing "abscess cavity" with air-fluid level. The irregularity on the medial aspect of the cavity is suggestive of tumor. A. F. I. P. Acc. No. 218737–135.

Figure 80. Cut surface of the tumor the roentgenogram of which is seen in figure 79. Although the lateral and superior parts of the cavity appear to have a thin wall, it is lined by tumor tissue throughout. A mass of tumor tissue thickens and obstructs the bronchus medially and accounts for the irregularity seen in the roentgenogram. A. F. I. P. Acc. No. 218737–4.

Fig. 77

Fig. 78

Fig. 79

Fig. 80

THORACIC INLET TUMORS. At the upper thoracic inlet, infiltrating tumors produce a complex of symptoms known as "superior pulmonary sulcus syndrome." Bronchogenic carcinoma is by far the most common cause of the syndrome, although the rare primary branchial cleft tumors, sympathicoblastomas of the cervical ganglia, osteogenic sarcomas, and metastatic tumors can be responsible, as can noncancerous conditions such as infiltrating and organizing tuberculosis. Most of the cancers responsible for the syndrome are of the well differentiated squamous cell type—the type most prone to invade the wall of the thorax by direct extension (fig. 82). Carcinomas that may begin in the metaplastic epithelium of tuberculous lesions have direct access to the region under discussion. The subject has recently been reviewed by Herbut and Watson, who collected 134 instances and added 17 of their own, making a total of 151 cases, three fourths of which were associated with carcinomas of the lung. Horner's syndrome occurred in all but one, and there was loss of power in the arm in 99 patients, destruction of ribs in 72, destruction of vertebrae in 41, and edema of the arm in 20.

GROSS. Tumors are more frequent in the upper lobes in a ratio of almost six to four. Fifty-three percent occur on the right side. A classification based on the location of the tumor in the bronchus is as follows:

1. Central: involving the stem or first division bronchi (65 percent).
2. Segmental: involving the segmental bronchi (23 percent).
3. Peripheral: involving small peripheral bronchi (12 percent). In this category the tumor is usually based on the pleura.
4. Multiple: involving any of above three in combination or multiple tumors arising in bronchi in any one category.

It is not possible to predict the histologic type with certainty from the location of the tumor, but certain generalizations can be made if it is kept in mind that many exceptions exist (see Koletsky). When the tumor is proximal to the bifurcations of the main stem bronchi, it is most likely to be of the anaplastic type. The squamous lesion, although likewise usually central in origin, often begins peripheral to the first bifurcation (figs. 72, 73). There is some predominance of adenocarcinoma in the peripheral group.

Some bronchogenic tumors begin in an infiltrative fashion within the mucosa, with only slight stenosis of the lumen and little or no extension into the surrounding parenchyma. These may produce severe symptoms, especially cough, but are relatively difficult to detect bronchoscopically, since the mucosa may appear only reddened and slightly granular (figs. 74, 75, 88). The anaplastic tumors especially may possess this characteristic, although it is uncommon for all types. Much more frequent is the bulky tumor that not only occludes the bronchus but extends into the surrounding tissue as a large expanding and infiltrating mass (fig. 73). In the tissue distal to the central type, there is usually an organizing pneumonitis that is responsible for much of the symptomatology associated with these tumors, and that is not always grossly

distinguishable from the tumor. Most likely to be clinically silent is the peripheral lesion (fig. 76), since there is less pneumonic tissue beyond it, and since from its distance from the major bronchi it is less likely to be associated with cough until the pleura has finally become involved.

The bronchial tumors consist of translucent grey-pink tissues, which are often flecked with black anthracotic material near the periphery. Yellow, opaque flecks are common especially in the squamous cell tumors. Necrosis is common in the bulky tumors. The liquefaction of the necrotic tissue forms cavities in from 10 to 30 percent of carcinomas (figs. 77–80). These cavities may attain considerable size, as in Koletsky's experience, where 19 of his 100 cases had cavities in excess of 4 cm. in diameter. The cavities occur most frequently in the squamous cell tumors and are least common in the anaplastic lesions, with the adenocarcinomas intermediate in incidence. The cavity is almost always completely surrounded by tumor, and it is relatively rare to find an actual abscess cavity in the pneumonic tissue beyond the tumor. When ulcerative tuberculosis or lung abscess coexists with carcinoma, the tumor cells may spread along the walls of cavities.

Vigorously growing neoplasms require an abundant supply of oxygenated blood. In the lung such blood is supplied by the bronchial arteries, and these vessels become enlarged in carcinoma of the lung, forming a rich plexus within the neoplastic tissue (pl. II–A, B). Fatal hemorrhage occurs in from one to three percent of carcinomas of the lung.

MICROSCOPIC. For convenience malignant epithelial bronchogenic tumors of the lung will be classified on the simplest possible histologic basis:

1. Epidermoid carcinoma.
2. Anaplastic carcinoma.
3. Adenocarcinoma.
4. Mixed forms combining any or all of the preceding cell types.

The relative incidence of the carcinomatous tumors as stated by various observers depends largely on definitions. In the above classification the "round-cell" and "oat-cell" tumors have been grouped with the anaplastic tumors. Those definitely recognizable as squamous cell tumors by virtue of keratinization, presence of intercellular bridges, etc., comprise between 45 and 60 percent of all malignant epithelial tumors of the lung. Adenocarcinomas occur in between 9 and 12 percent, and the rest are anaplastic tumors. The range in percentages allows for the classification of combined forms and for differences in usage by various authorities. When very large sections or numerous blocks are studied, the incidence of mixed tumors is indeed high. Classification according to the predominating tissue, however, yields useful correlations with the age and sex of the patient and the clinical course. Some of the tumors present so intimate an admixture, for example of squamous and acinar forms, that some such descriptive term as "adenocarcinoma with squamous cell changes" may be applied until the natural history of these lesions becomes better known (figs. 98, 99).

BRONCHOGENIC CARCINOMA

(Figures 81 and 82 are from the same case)

Figure 81. Peripheral epidermoid carcinoma with invasion of the thoracic wall. This roentgenogram shows a spherical shadow in the right upper lobe. A. F. I. P. Acc. No. 218737–136.

Figure 82. Surgical block dissection of the thorax included a rib. Histologic section of the tumor, the cut surface of which is illustrated, revealed a very well differentiated squamous cell carcinoma. A. F. I. P. Acc. No. 218737–137.

Figure 83. Histologic section of a well differentiated squamous cell carcinoma from a peripherally situated pulmonary tumor. A. F. I. P. Acc. No. 218737–138.

Fig. 81

Fig. 82

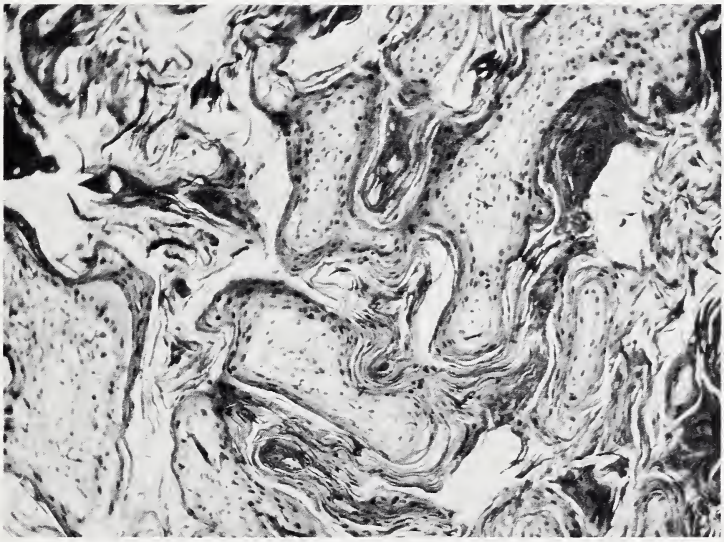

Fig. 83

BRONCHOGENIC CARCINOMA

(Figures 84–86 are from the same case)

Figure 84. Epidermoid carcinoma of the lung. A. F. I. P. Acc. No. 218737–143.

Figure 85. Another field from tumor illustrated in figure 84, demonstrating pleomorphism. Here the cells are largely spindle-shaped. A. F. I. P. Acc. No. 218737–144.

Figure 86. Tumor giant cells and other bizarre forms from another portion of the tumor illustrated in figures 84 and 85. A. F. I. P. Acc. No. 218737–145.

Figure 87. "Cancerous pneumonia." Carcinoma cells have been aspirated into alveoli distal to a bronchogenic tumor. The interalveolar septa are thickened. Some of the cuboidal lining cells of the alveoli have been replaced by the more darkly staining neoplastic elements. A. F. I. P. Acc. No. 218737–49.

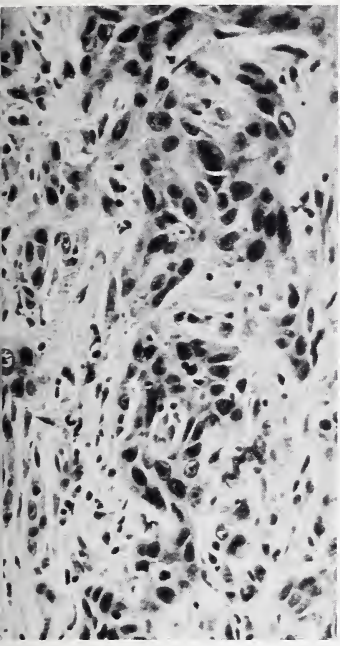

Fig. 84

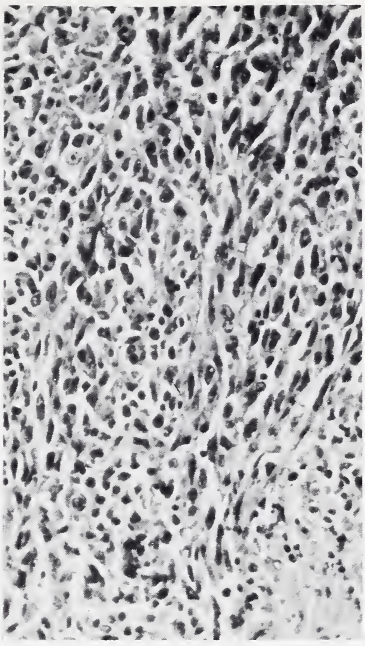

Fig. 85

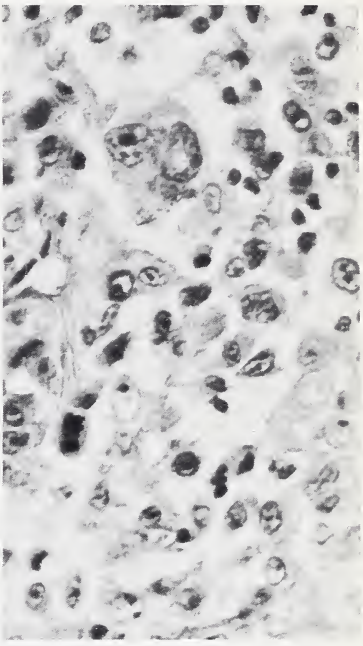

Fig. 86

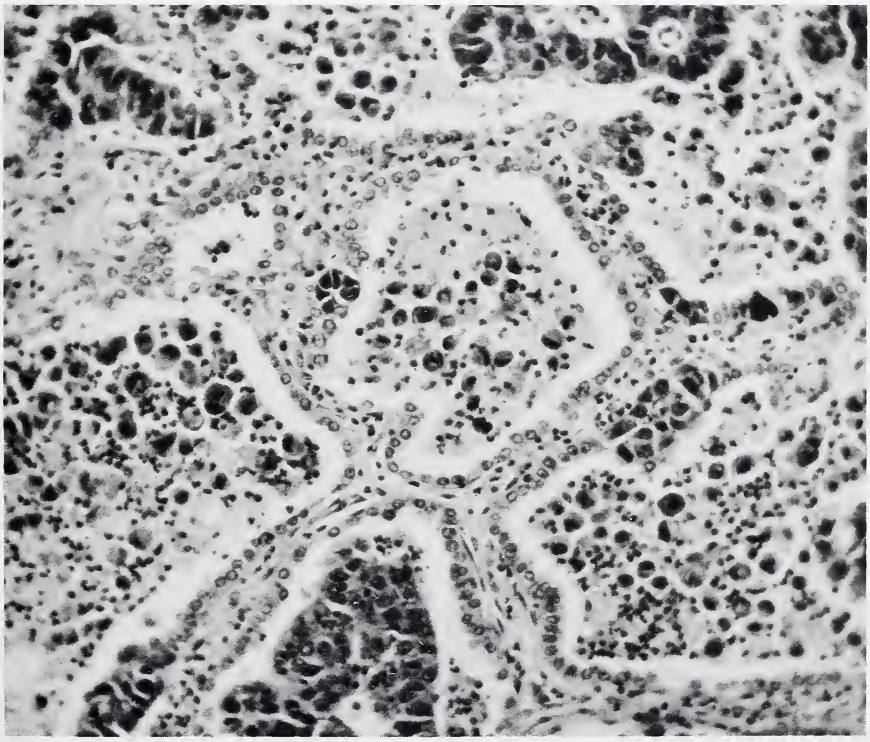

Fig. 87

PLATE II

A. Bronchovascular cast showing blood supply of carcinoma of the lung. Specimen viewed from the rear. The tumor arose in a tuberculous cavity (CAV.) at the apex of the left lung. The aorta (AO.) has been injected with black plastic and curves obliquely downwards to the right. The black plastic extended into a plexus of fine vessels and now remains as a vascular skeleton, after digestion of the tissue. The pulmonary artery is labelled P. A. Bronchial tree is injected with white, and pulmonary arteries and veins are injected with red and green plastic respectively. (This is figure 2—black and white—from Liebow, A. A., Hales, M. R., Harrison, W., Bloomer, W., and Lindskog, G. E. The genesis and functional implications of collateral circulation of the lungs. Yale J. Biol. & Med., 22: 637–650, 1950.) A. F. I. P. Acc. No. 218737–160.

B. Bronchovascular cast injected as in the preceding specimen. A roughly spherical space remains after the spherical epidermoid tumor was digested away. In its depths can be seen, in black, the greatly enlarged bronchial arteries. The stem bronchus of the right lower lobe has been flattened into ribbon as have bronchi and pulmonary arteries and veins at the periphery of the tumor. A. F. I. P. Acc. No. 218737–161.

A

B

PLATE II

In some instances of epidermoid carcinoma there is a very gradual transition between atypical metaplastic epithelium and carcinoma (figs. 68, 69). Relatively little is known about preinvasive carcinoma (carcinoma in situ) in the bronchi. An excellent study of atypical bronchial epithelium has been made by Lindberg. The best differentiated tumors resemble those of the skin and show evidence of keratinization with epithelial pearls (fig. 83). Such tumors are in the minority and most epidermoid tumors, while retaining the characteristics of the type, display little keratinization. The distinction between the less differentiated epidermoid tumors and the anaplastic carcinomas is arbitrary. In some generally well differentiated tumors, there may be some anaplastic tissue, and the reverse may also be observed. The primary pulmonary tumor may be more or less differentiated than the metastases.

Some epidermoid tumors manifest a tendency toward extreme pleomorphism, with portions consisting of spindle-shaped cells resembling sarcoma, and areas in which multinucleated tumor giant cells may be present (figs. 84–86). Some lesions have actually been considered as carcinosarcomas (Bergmann, Ackerman, and Kemler).

In the anaplastic group are included tumors referred to as "oat-cell carcinoma," "round-cell carcinoma," "small-cell carcinoma," or "spindle-cell carcinoma." The component cells of some of these lesions resemble lymphocytes in size and shape, in the scanty basophilic cytoplasm of the component cells, and in the dense reticular structure of the nucleus (fig. 90). Others possess larger, more ovoid, or spindle-shaped cells. In the latter type, palisading at the margins of the groups of tumor cells often occurs (fig. 89). Characteristically, the nucleoli are small but multiple. Mitoses are numerous. There is a striking tendency to spread within the intrapulmonary as well as within the extrapulmonary lymphatics (fig. 88). Forms transitional to other types of carcinoma occur.

The chief differentiating point between adenocarcinomas, even the less differentiated forms which possess only occasional acini, and the epidermoid or anaplastic varieties is the presence of mucus as demonstrated by appropriate staining with Mayer's mucicarmine. Little is gained by further subclassification of these tumors into "papillary," "clear cell," and other forms (figs. 100–105). Calcification may rarely be in evidence in the papillary form (fig. 102). Occasionally, there is found an adenocarcinoma with squamous cell changes as in carcinoma of the uterus. They may represent the malignant counterpart of the mucoepidermoid variant of the cylindroid form of adenoma of the bronchus (figs. 98, 99). Forms transitional to the anaplastic "oat-cell" tumors also exist. Very pleomorphic cell types may be seen in tumors predominantly adenocarcinomatous as in the others.

EXTENSION AND METASTASIS. Squamous cell tumors spread chiefly by direct extension, and lymph nodes are invaded rather than reached by lymphatic permeation; blood vessels likewise are invaded (fig. 77). When a

BRONCHOGENIC CARCINOMA

Figure 88. Anaplastic carcinoma apparently originating in the right main stem bronchus. The tumor has spread by way of the lymphatics distally about the bronchovascular rays and septa into the pleura, and proximally into the trachea, the lining membrane of which is roughened. A large mass of tumor is visible beneath the carina. The left lung showed no gross tumor. A. F. I. P. Acc. No. 218737–146.

Figure 89. Anaplastic carcinoma. Ovoid and spindle-shaped cells predominate. There is palisading at the margin of the cell masses. Numerous mitoses are present. A. F. I. P. Acc. No. 218737–147.

Figure 90. Anaplastic carcinoma. "Small round cells" somewhat resembling lymphocytes predominate. A. F. I. P. Acc. No. 218737–148.

Fig. 88

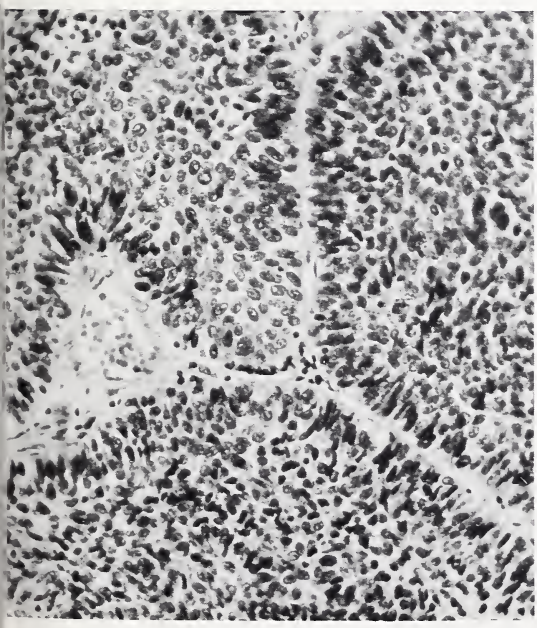

Fig. 89

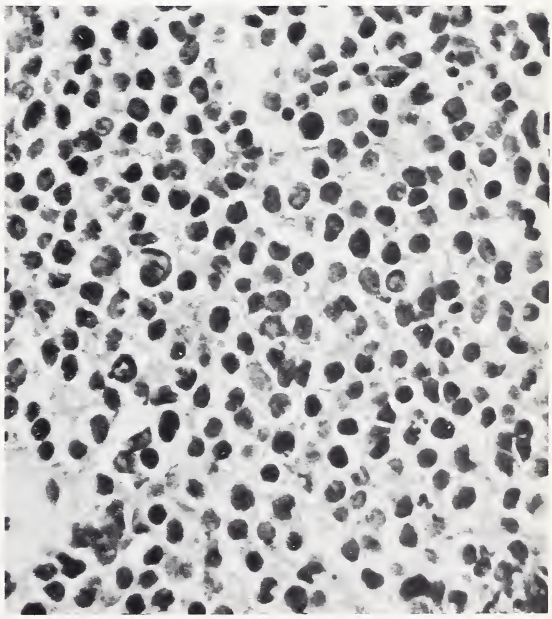

Fig. 90

ADENOCARCINOMA, POSSIBLY OF MUCOUS GLAND ORIGIN

(Figures 91–97 are from the same case)

Figure 91. Roentgenogram made during routine survey of hospital employees, demonstrating shadow of tumor illustrated in figure 92. There were no symptoms. A. F. I. P. Acc. No. 218737–149.

Figure 92. Carcinoma, possibly of mucous gland origin, in subapical bronchus of right upper lobe. There are no features that would in the gross distinguish this lesion from other types of carcinoma. A. F. I. P. Acc. No. 218737–150.

Figure 93. Histologic section of tumor shown in figure 92. Columnar arrangement of neoplastic cells, with hyaline stroma, suggesting that seen in some "mixed tumors" of the salivary glands. × 52. A. F. I. P. Acc. No. 218737–152.

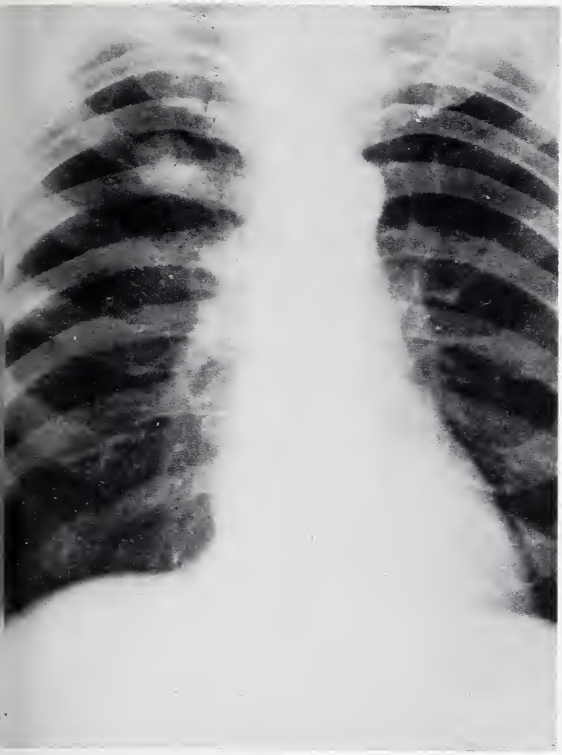

Fig. 91

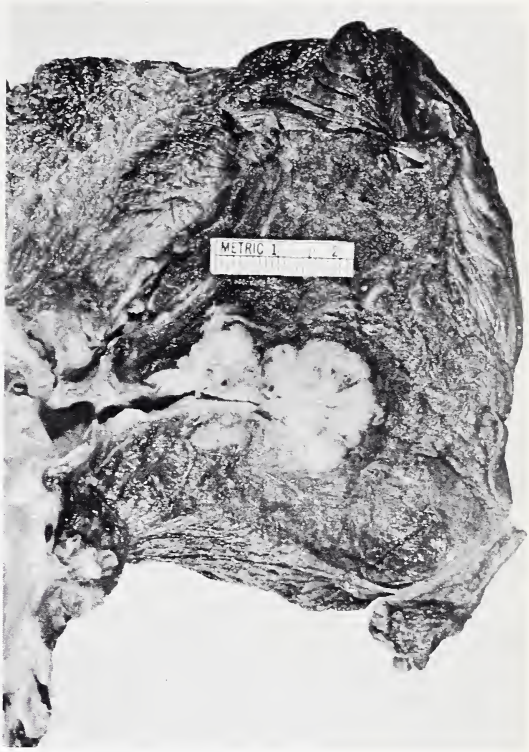

Fig. 92

Fig. 93

ADENOCARCINOMA, POSSIBLY OF MUCOUS GLAND ORIGIN

(Figures 91–97 are from the same case)

Figure 94. Histologic section of margin of tumor shown in figure 92. Groups of tumor cells within the mucosa whose covering ciliated epithelium is intact (see figure 95). Their appearance suggests neoplastically transformed mucous glands, and their position is compatible with such an origin. A. F. I. P. Acc. No. 218737–151.

Figure 95. Detail of figure 94. There are small, fairly regular cells in groups with hyaline interstitial material. Figure 93 demonstrates the result of further accumulation of the latter. The basement membranes are still visible. A. F. I. P. Acc. No. 218737–153.

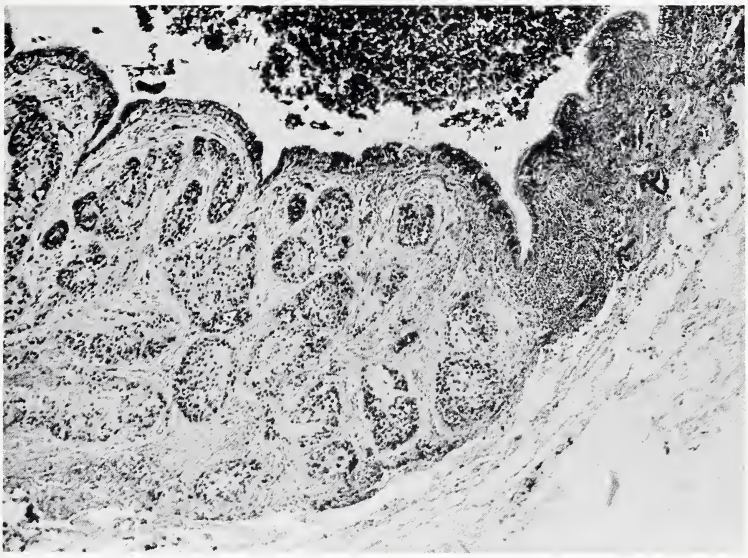

Fig. 94

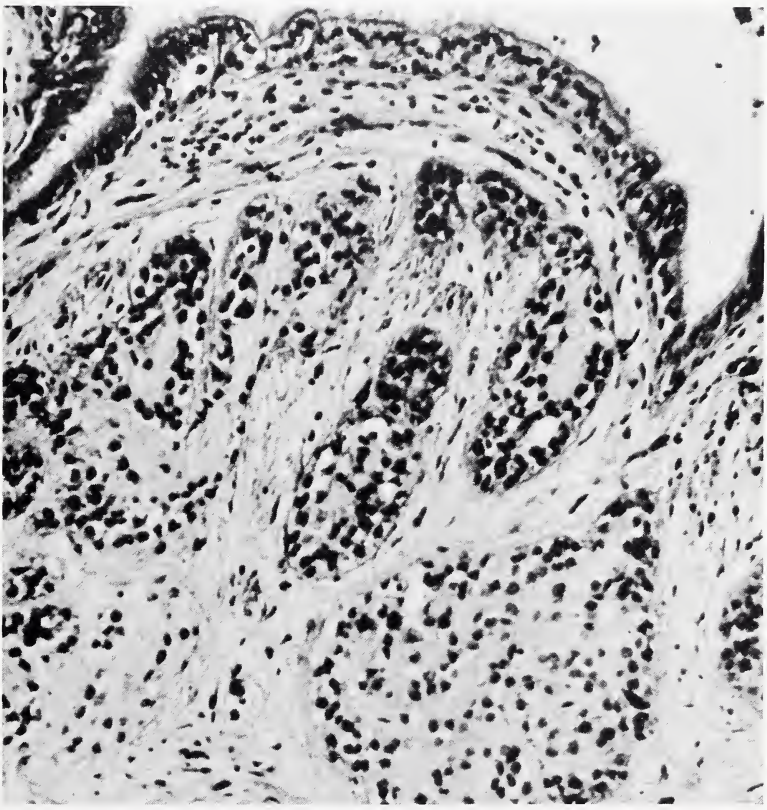

Fig. 95

ADENOCARCINOMA, POSSIBLY OF MUCOUS GLAND ORIGIN

(Figures 91–97 are from the same case. Figures 98 and 99 are from the same case)

Figure 96. Histologic section from another portion of the tumor illustrated in figure 92. The epithelium has a more anaplastic character and no basement membranes can be discerned. The stroma is densely fibrous. A. F. I. P. Acc. No. 218737–154.

Figure 97. Detail of figure 96. The appearance, despite anaplasia, is compatible with that of certain carcinomas of salivary gland origin. A. F. I. P. Acc. No. 218737–155.

Figure 98. Histologic section of a bronchogenic carcinoma with an uncommon microscopic pattern. There is an intimate admixture of mucous and squamous epithelium. The spaces contain material staining positively with mucicarmine. This tumor is from the collection at the Armed Forces Institute of Pathology and is there classified as a "muco-epidermoid carcinoma." Compare with figure 57. × 55. A. F. I. P. Acc. No. 292766–1.

Figure 99. Higher magnification of slide illustrated in figure 98. The two types of epithelial cells are intimately admixed but sharply demarcated. × 205. (From the Armed Forces Institute of Pathology.) A. F. I. P. Acc. No. 292766–2.

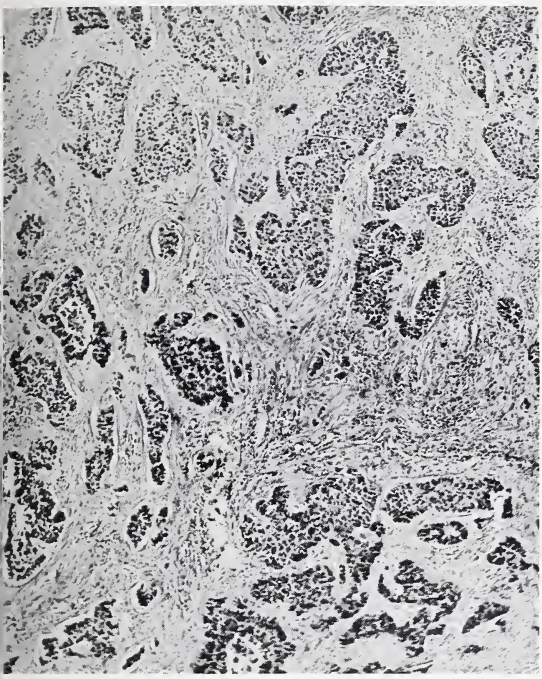

Fig. 96

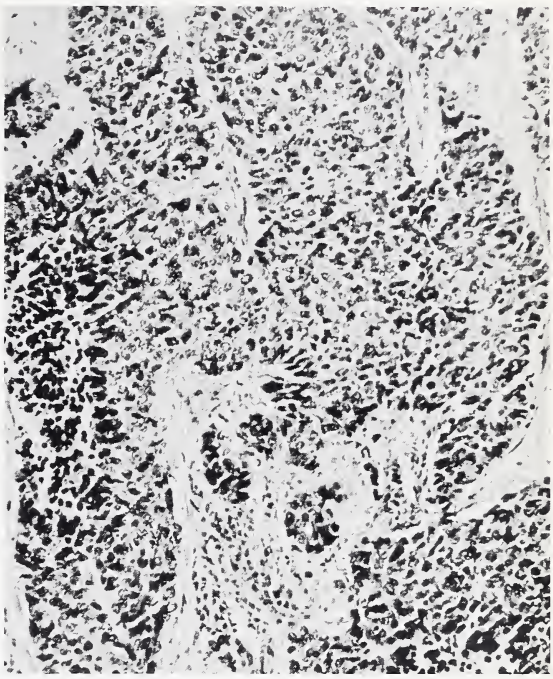

Fig. 97

Fig. 98

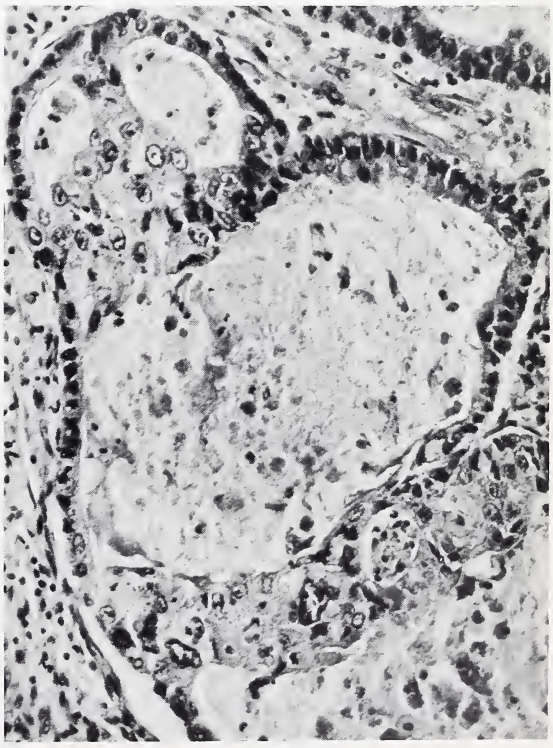

Fig. 99

BRONCHOGENIC CARCINOMA

(Figures 100–102 are from the same case)

Figure 100. Adenocarcinoma of posterior basal bronchus of right lower lobe. The tumor has a pearly translucency, and shows no necrosis. A. F. I. P. Acc. No. 218737–156.

Figure 101. Histologic section from tumor illustrated in figure 100. The lining membrane of the bronchus has been transformed, and the deeper tissue invaded. A. F. I. P. Acc. No. 218737–157.

Figure 102. Histologic section from another area of the tumor illustrated in figure 100. There is calcification in the stroma. Such deposits were rare. A. F. I. P. Acc. No. 218737–158.

Figure 103. Adenocarcinoma of bronchus. The irregular acinar structures are filled with mucus, although relatively few of the neoplastic elements have the appearance of goblet cells. A. F. I. P. Acc. No. 218737–159.

Fig. 100

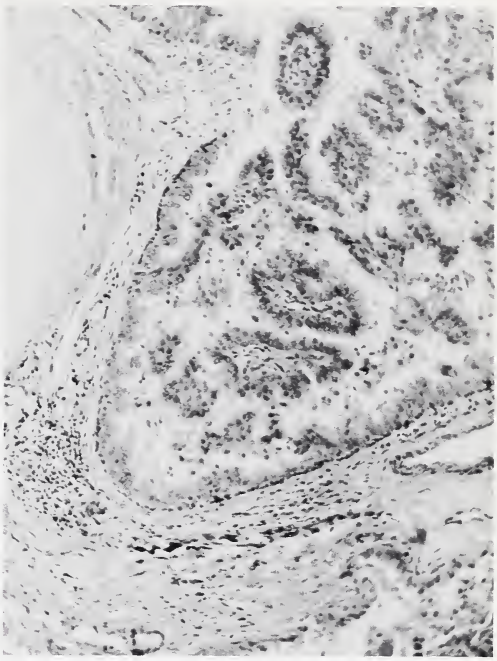

Fig. 101

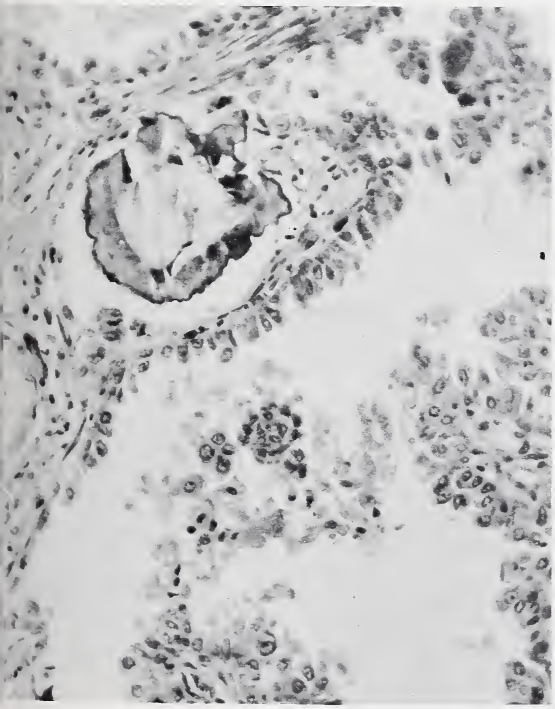

Fig. 102

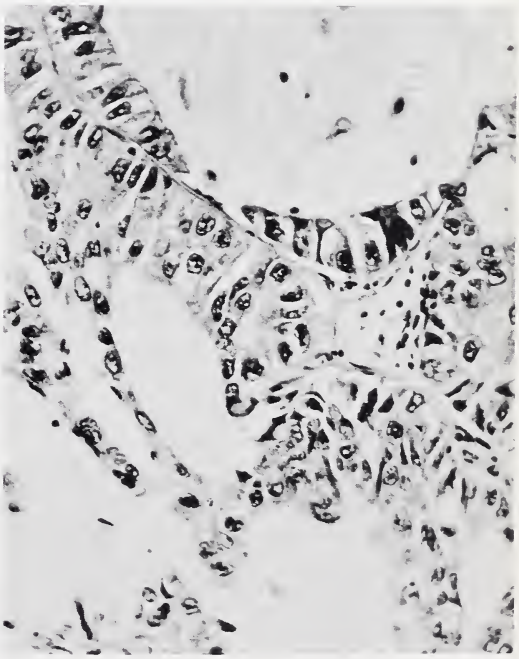

Fig. 103

BRONCHOGENIC CARCINOMA

(Figures 104 and 105 are from the same case)

Figure 104. Adenocarcinoma of bronchus, metastatic in lymph node. Definite acini are formed, some of which contain grumous material with cholesterol clefts. (Compare with figure 102.) × 125. A. F. I. P. Acc. No. 218737–37.

Figure 105. Histologic section of the primary tumor the metastasis of which is shown in figure 104. Here the tumor is of the type referred to as "clear cell" by some pathologists. The cells occur in rounded masses. Some mitoses are visible in the field illustrated. × 280. A. F. I. P. Acc. No. 218737–56.

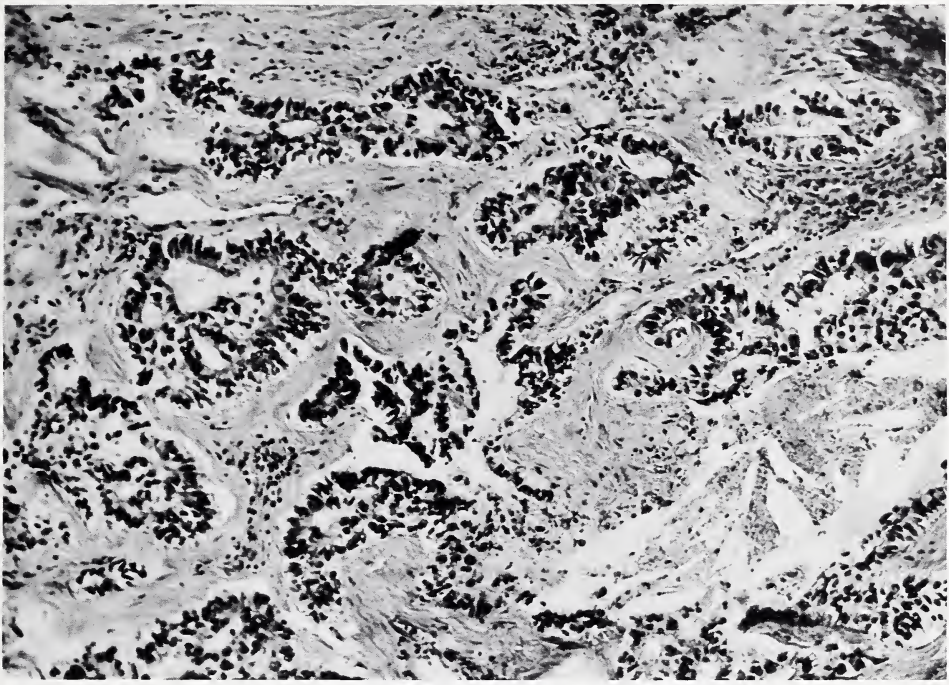

Fig. 104

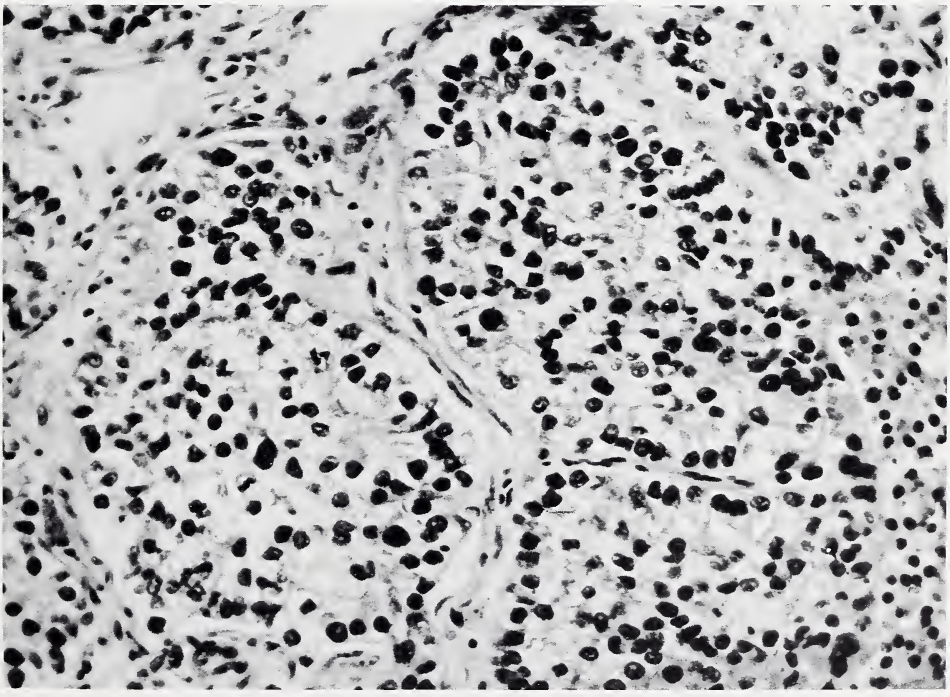

Fig. 105

lung tumor is found to invade the wall of the thorax, it is most likely to be of the squamous cell type (figs. 82, 83). Anaplastic tumors spread chiefly by lymphatics both within (fig. 88) and outside of the lung, and adenocarcinomas chiefly by blood stream, although they do not neglect the lymphatics. Numerous exceptions exist. Thus, a well differentiated squamous cell tumor may become widely disseminated by invading a pulmonary vein. Spread of carcinoma may occur also by bronchial embolism with resulting "cancerous pneumonia" (fig. 87), or isolated nodules in such position as to suggest aspiration into a dependent bronchus.

TABLE I. CARCINOMA OF THE LUNG

INCIDENCE OF METASTASES IN VARIOUS SITES

Organ	Ochsner & DeBakey* (3,047 collected cases) Percent	Fried** (319 pts.) Percent
Regional lymph nodes	72.2	81.00
Liver	33.3	40.06
Bones	21.3	40.04
Adrenals	20.3	38.00
Kidneys	17.5	20.03
Brain	16.5	11.01
Heart and pericardium	12.7	9.03
Pancreas	7.3	6.35

*Reprinted from Ochsner, A., and DeBakey, M. Significance of metastasis in primary carcinoma of the lung. J. Thoracic Surg., 11:357–387, 1942.

**Reprinted from Fried, B. M. Bronchiogenic Carcinoma and Adenoma. Baltimore: Williams & Wilkins, 1948.

The spread of carcinoma proximally in the bronchial wall, a problem of prime importance in resective surgery, has been studied by Griess, McDonald, and Clagett, who found that extension of tumor proximally was more frequent in squamous cell carcinoma (10 out of 16 cases), but when extension occurred

in adenocarcinoma (3 out of 6 cases) it extended further. The furthest extension in a case of adenocarcinoma was 2 cm. from the grossly visible margin of tumor. The extension in this case was probably further than 2 cm. as the tumor was divided at the same level as the bronchus. Study in a larger number of cases is necessary on this problem.

The pulmonary ligament likewise contains tissue continuous with the adventitial coats of the structures in the hilum. Adhesions may also contain lymphatics carrying metastases from a peripherally situated tumor (Ochsner and DeBakey, 1942). In Koletsky's autopsy series the incidence of extrathoracic metastases was least in squamous tumors (35 percent) and much higher in the adenocarcinomas (86 percent) and anaplastic "small-cell" tumors (89 percent). Björk found in a clinical series that the incidence of metastases, including intrathoracic lymph node extensions, at the time of admission was only slightly lower in the squamous group and that peripheral tumors metastasized no later than central tumors.

The most frequent sites of metastases are indicated in data derived from two large series (table I).

DIAGNOSTIC METHODS. In addition to bronchoscopic biopsy and biopsy of presumed metastatic sites, three important methods have been employed as accessories in obtaining a histologic diagnosis of cancer of the lung: examination of material obtained by aspiration of tissue through the wall of the chest, examination of pleural fluid, and examination of sputum or bronchial secretions.

The aspiration biopsy has yielded excellent results in some hands (Gledhill, Spriggs, and Binford), although others have stressed the dangers of introducing the needle through the wall of the thorax into a possibly infected and highly vascular tumor, or the parenchyma itself. Acknowledging the dangers, this procedure has its greatest use in the diagnostic approach to peripheral pulmonary lesions, and to the large inoperable tumors inaccessible to the bronchoscope where it is desired to establish the diagnosis before the institution of radiation therapy.

The examination of pleural fluid whether by interpretation of sections from embedded centrifugates or of direct smears demands great care if false positive diagnoses are to be avoided. Since the statistical incidence of carcinoma of the lung is high in those in whom this procedure is carried out, it is no doubt true that the correct diagnosis has been made on the basis of entirely false criteria. Mesothelial cells in rapid proliferation can be extremely bizarre as illustrated in instances of rheumatic fever, lupus erythematosus, and organizing exudates of any sort (fig. 106). Cells in large clumps (fig. 110), anisocytosis, multinucleated cells (fig. 107), eccentric nuclei, signet ring cells, fat-filled elements, and mitoses (figs. 106, 109), even those of atypical structure, may all occur in noncancerous exudates. Cells with large nuclei and atypical

ATYPICAL PROLIFERATION OF MESOTHELIAL CELLS

(Figures 108–110 are from the same case)

Figure 106. Histologic section of epicardium showing organizing pericarditis from a patient with lupus erythematosus. Note the two mesothelial cells in mitosis and the bizarre giant cell. A. F. I. P. Acc. No. 218737–162.

Figure 107. Sediment of aspirated pleural fluid from a patient with organizing pleurisy. The nuclei of the proliferated mesothelial cells vary markedly in size, shape, and chromatin content. Note the multinucleated giant cell and prominent nucleoli. A. F. I. P. Acc. No. 218737–163.

Figure 108. Sediment of aspirated pleural fluid from a patient with organizing pleurisy. There is marked variation in the size and shape of proliferated mesothelial cells. A. F. I. P. Acc. No. 218737–165.

Figure 109. Another field from the same fluid illustrated in figure 108. A cell in mitosis is seen in the middle of the proliferated mesothelium. A. F. I. P. Acc. No. 218737–166.

Figure 110. Another field from the same fluid illustrated in figures 108 and 109. Note the very large mass of mesothelial cells. A. F. I. P. Acc. No. 218737–164.

Fig. 106

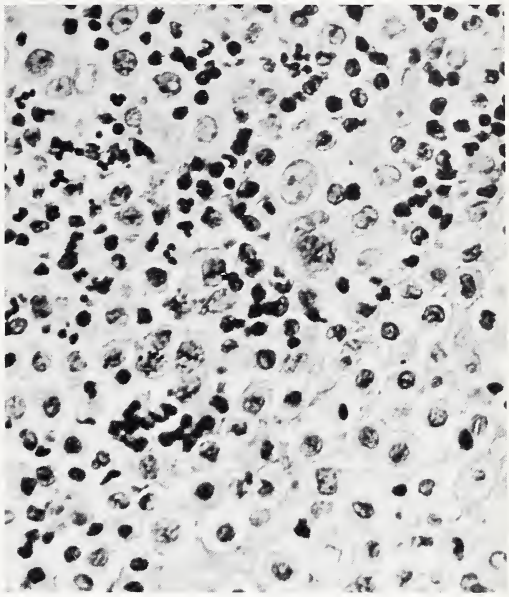

Fig. 107

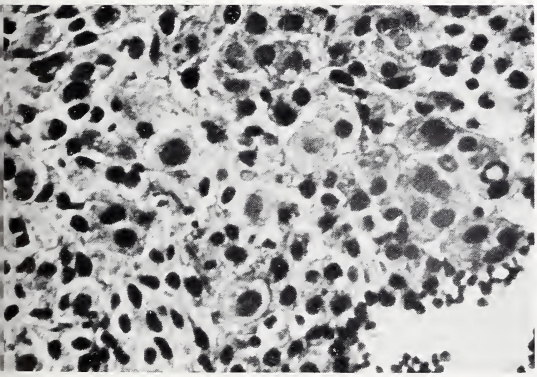

Fig. 108

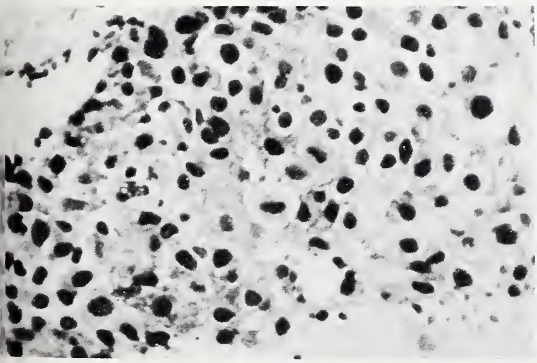

Fig. 109

Fig. 110

MALIGNANT CELLS IN PLEURAL FLUID

(Figures 111 and 112 are from the same case. Figures 113 and 114 are from the same case. Figures 115–117 are from the same case)

Figure 111. Histologic section of neuroblastoma, metastatic in lymph node. (Compare with figure 112.) A. F. I. P. Acc. No. 218737–167.

Figure 112. Cells from metastatic neuroblastoma in a sediment of pleural fluid. The variable small cells in the mass have scanty cytoplasm and finely reticular nuclei with many minute nucleoli. A. F. I. P. Acc. No. 218737–168.

Figure 113. Histologic section of pleura, necropsy specimen, showing invasion by cells of a reticulum cell sarcoma. (Compare with figure 114.) A. F. I. P. Acc. No. 218737–169.

Figure 114. Cells from metastatic reticulum cell sarcoma in sediment of pleural fluid. The irregular cells have shrunk away from the protein material of the fluid. The cells vary in size and shape as do their nuclei. Some are ovoid or spindle-shaped. Nucleoli are prominent. A. F. I. P. Acc. No. 218737–170.

Figure 115. Cells from metastatic adenocarcinoma of the breast in sediment of pleural fluid. An acinar configuration is assumed by the tumor cells which have a deeply acidophilic cytoplasm and nuclei with prominent cell membranes and nucleoli. These cells stand out strikingly against the background of mesothelial cells and leucocytes. A. F. I. P. Acc. No. 218737–171.

Figure 116. Sediment from pleural fluid from the same patient as the sediment illustrated in figure 115. The neoplastic cells are in a berry-like cluster. A. F. I. P. Acc. No. 218737–172.

Figure 117. Sediment from pleural fluid from the same patient as the sediments illustrated in figures 115 and 116 showing another mass of neoplastic cells in acinar arrangement. A. F. I. P. Acc. No. 218737–173.

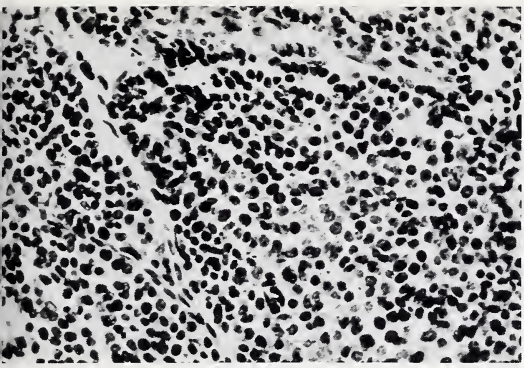

Fig. 111

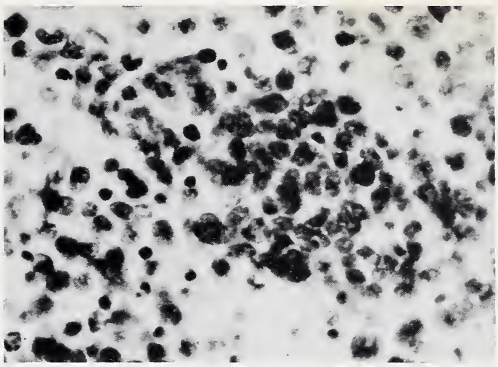

Fig. 112

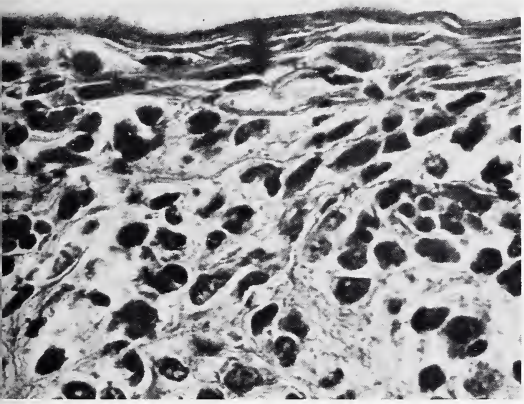

Fig. 113

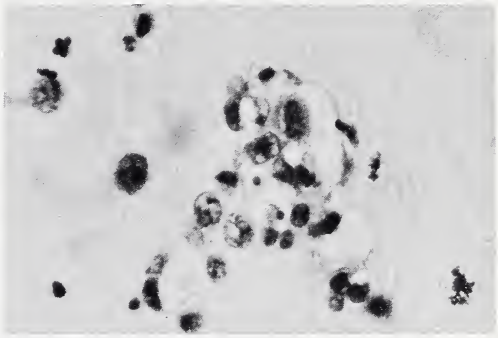

Fig. 114

Fig. 115

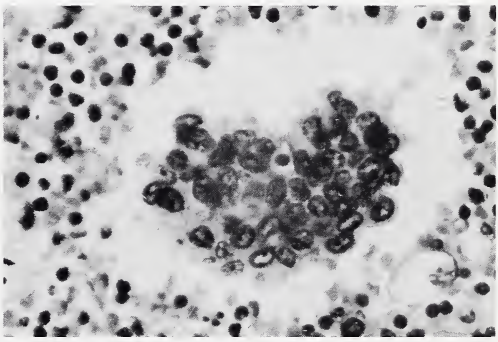

Fig. 116

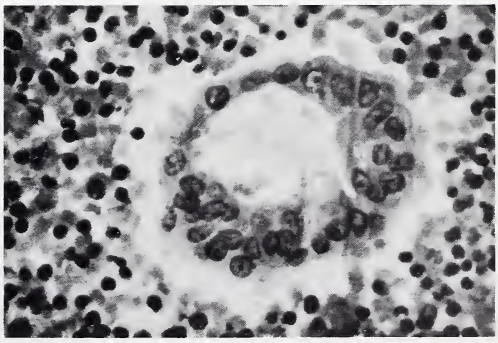

Fig. 117

MALIGNANT CELLS IN PLEURAL FLUID

(Figures 118–120 are from the same case. Figures 121–123 are from the same case)

Figure 118. Adenocarcinoma of lung invading the pleura as seen in biopsy specimen removed at operation. A. F. I. P. Acc. No. 218737–174.

Figure 119. A mass of vacuolated atypical cells in sediment of pleural fluid obtained preoperatively from the same patient whose biopsy specimen is illustrated in figure 118. The enormous size and variability of these cells distinguish them from adjacent mesothelial elements. A. F. I. P. Acc. No. 218737–175.

Figure 120. Another field from the same slide shown in figure 119. The neoplastic cells retain a columnar form and have a vacuolated, mucus-filled cytoplasm. A. F. I. P. Acc. No. 218737–176.

Figure 121. A mass of atypical cells from pleural fluid sediment of a patient with adenocarcinoma of the large intestine metastatic to the pleura. A. F. I. P. Acc. No. 218737–177.

Figure 122. Another group of cells from the same specimen illustrated in figure 121. One of the cells is in mitosis. A. F. I. P. Acc. No. 218737–178.

Figure 123. Mucus-producing cells in acinar arrangement from the same specimen illustrated in figures 121 and 122. A. F. I. P. Acc. No. 218737–179.

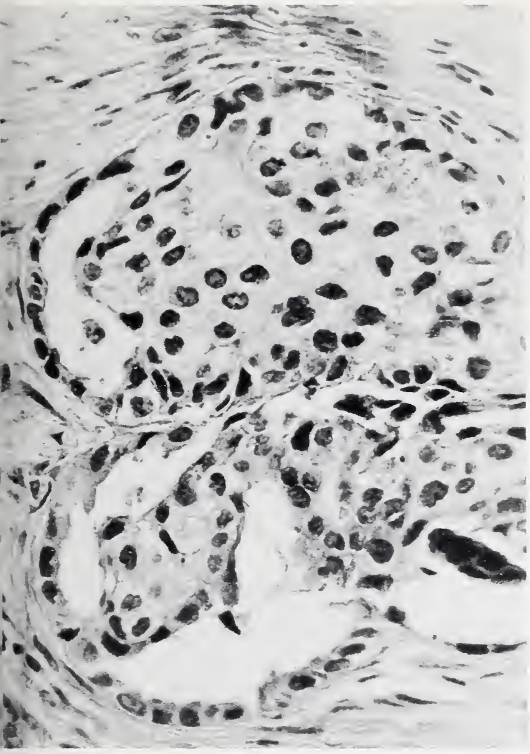

Fig. 118

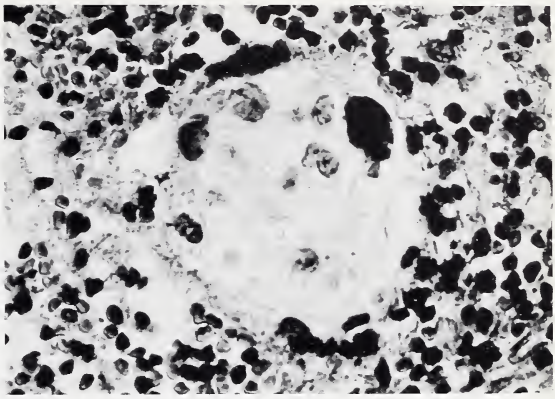

Fig. 119

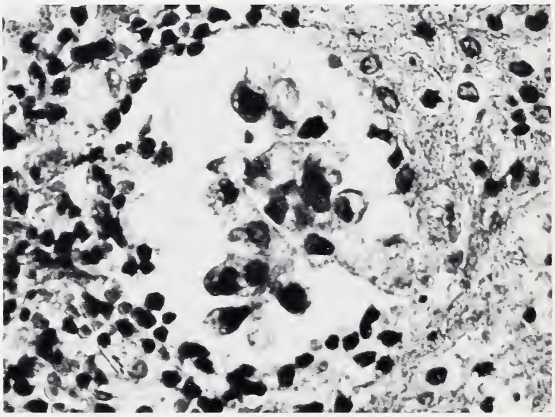

Fig. 120

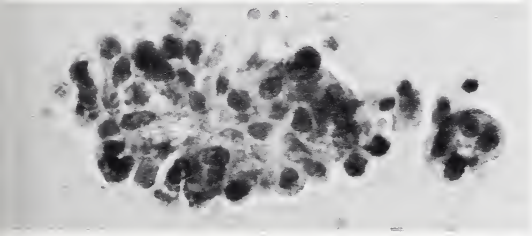

Fig. 121

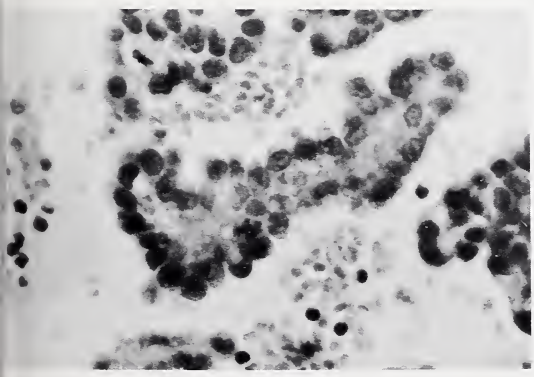

Fig. 122

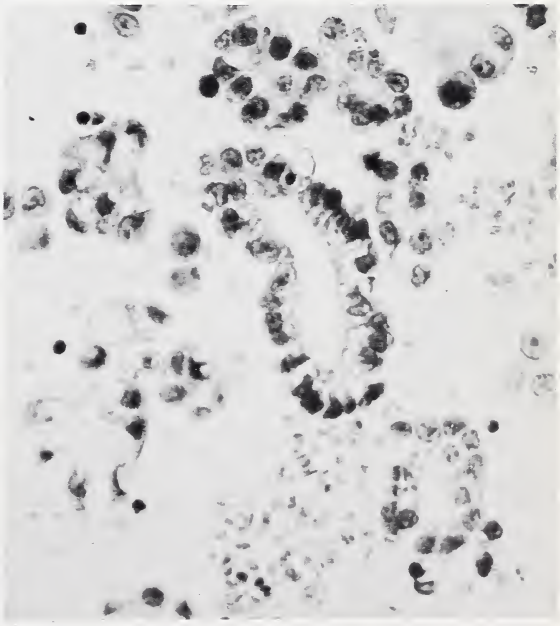

Fig. 123

mitoses are uncommon in such exudates, but they may occur. An organoid arrangement of atypical cells, especially in the rare instances when stroma is present, and the presence of specific materials, as for example mucus (figs. 120, 123) within the cells, are the best criteria for the diagnosis of cancer. Cell groups that stand out sharply against the generality of mesothelial and leukocytic elements are suggestive, so that even sarcomatous tumors may be distinguished on occasion (figs. 111–114). When the groups of atypical cells possess an acinar arrangement, carcinoma should be considered (figs. 115–117, 123). Strips of mesothelium may, however, curl upon themselves to present a misleading acinar aspect. It must also be remembered that mucus-producing epithelium may gain access to the pleural cavity via a bronchopleural fistula. The cytology of pleural fluid still requires intensive study, and enthusiastic reports should be subjected to critical statistical scrutiny.

Examination of sputum and bronchial secretions for tumor cells has proved very useful when well trained personnel is available. The preparation of direct smears for staining with the Papanicolaou or H & E techniques is less cumbersome and time-consuming than the preparation of histologic sections of embedded material, and very satisfactory results have been obtained with this latter method. In order to be useful, the interpretation of smears should be made objectively with no knowledge of the clinical history or even the age of the patient; otherwise, prejudicial extraneous criteria are introduced. This is an attitude of mind that is especially important during the period needed to acquire the skill to make reliable interpretations. Such training is most efficiently carried on under the supervision of someone already well acquainted with the pitfalls of the technique. There should then be a self-evaluation for the purpose of obtaining an estimate of the sensitivity of the method and of the incidence of false positive diagnoses. This evaluation requires not only the objective approach, but also a large amount of control material from noncancerous patients, especially from patients with bronchiectasis, lung abscess, tuberculosis, and organizing or lipoid pneumonia, diseases which have given the greatest difficulty in cytologic diagnosis.

Obviously, these criteria should also be applied in assessing the value of published work concerning the cytologic technique, and few tabulations can survive a critical survey. Also to be considered in the assessment are the numbers of specimens and the numbers of slides examined from each specimen, since there are limits to the practicability of the method. The sensitivity of the method (percentage of positive diagnoses in patients proved to have cancer) must be balanced against the number of false positive diagnoses, especially when the interpretation of the smears in the absence of other histologic evidence determines operative intervention. It has been claimed that over 90 percent of correct positive diagnoses can be made by examination of the sputum or bronchial secretions; but if the incidence of false positive diagnoses does not exceed 5 percent and there is no prejudicial foreknowl-

edge of the clinical data, then the incidence of correct positive diagnoses lies between 40 and 60 percent. It is clear from most of the reliable published reports that the number of positive microscopic diagnoses can be almost doubled over those produced by other techniques before the patient comes to operation. As to choice of materials, a single examination of bronchial secretions obtained from the bronchus draining a suspected lesion is more likely to yield a positive result than a single sputum examination. Since the sputum can, however, be obtained repeatedly without discomfort to the patient, a definite increment of positive diagnoses results from multiple examinations. Farber and his associates found that in a series of 110 proved cases of pulmonary cancer, when five samples of sputum were examined, a positive cytologic diagnosis was made in 87 percent. They also found that of the positive cytologic diagnoses 70 percent were made on the first smear. They recommend that three slides from each of five daily specimens be examined before a report is made.

The features diagnostic for malignancy are in general the same as those used in the interpretation of histologic sections, but the diagnosis is more difficult since stroma is lacking. It is hazardous to base the diagnosis on single cells, and clumps of cells should be the basis of judgment. Suggestive findings are variation in size and shape and staining properties of the cytoplasm and nucleus, hyperchromatism, and prominent nucleoli. Mitoses are rarely present in exfoliated cells (figs. 138, 144). Since it is sometimes feasible to distinguish even the type of tumor, descriptions of the most characteristic examples of each variety will follow, even though classification is often not possible.

The cells of well differentiated epidermoid tumors tend to possess sharp cell outlines. Adjacent elements may appear to overlap. The cytoplasm is often deeply acidophilic, a feature well brought out with the Papanicolaou technique. Very large cells may be found, but there are variations as is to be expected in any carcinoma. Epithelial pearls or other evidences of keratinization may be found (fig. 137). These may come also from metaplastic epithelium (fig. 131). The nuclei typically possess thick membranes and a coarse chromatin network with irregular clumping (figs. 135, 138). Metaplastic epithelium that has replaced the pseudostratified columnar form typically consists of more uniform cells with more finely reticular nuclei, and with less prominent cell membranes (figs. 133, 136). The distinction from carcinoma is difficult in some instances (fig. 136).

Cells from anaplastic carcinoma are typically small, closely crowded with frequently overlapping nuclei in berry-like clusters, and possess almost no cytoplasm (fig. 139). The nuclear structure is finely reticular, and within the fine mesh can be seen multiple minute nucleoli. There is considerable resemblance to lymphocytes or to clumps of epithelioid cells in tuberculous patients (fig. 128). The tumor cells tend to vary more in size and shape.

NON-NEOPLASTIC CELLS FROM SPUTUM

Figure 124. A group of mononuclear cells, showing some variation in size and shape. The cytoplasm is vacuolated. Nucleoli are minute. A. F. I. P. Acc. No. 218737–180.

Figure 125.* Multinucleated giant cell. × 600. A. F. I. P. Acc. No. 218737–181.

Figure 126. Large binucleated phagocyte with granules of anthracotic pigment in the cytoplasm. A. F. I. P. Acc. No. 218737–182.

Figure 127. Multinucleated giant cell with vacuolated cytoplasm. Nucleoli are prominent. This type of cell may be confused with desquamated cells from adenocarcinoma. Specimens containing such phagocytes usually contain forms transitional to more characteristic mononuclear phagocytes similar to those illustrated in figure 124. A. F. I. P. Acc. No. 218737–183.

Figure 128. This compact group of epithelioid cells might be confused with cells desquamated from an anaplastic carcinoma. The epithelioid cells vary less in size, however, and have denser more homogeneous nuclei. A. F. I. P. Acc. No. 218737–184.

Figure 129. A group of ciliated columnar epithelial cells. In the presence of artifacts, such as those produced when a specimen is allowed to dry before fixation, these cells may appear very atypical. Remnants of cilia should suggest normal epithelium. A. F. I. P. Acc. No. 218737–185.

Figure 130.* Squamous epithelium from structures of oral cavity, esophagus, or pharynx. ×410. A. F. I. P. Acc. No. 218737–186.

Figure 131. An "epithelial pearl," probably from metaplastic squamous epithelium. Such pearls are not pathognomonic of cancer. A. F. I. P. Acc. No. 218737–187.

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*Reprinted from Liebow, A. A., Lindskog, G. E., and Bloomer, W. E. Cytological studies of sputum and bronchial secretions in the diagnosis of cancer of the lung. Cancer, 1: 223–233, 1948. Figures 3 and 1 are our figures 125 and 130.

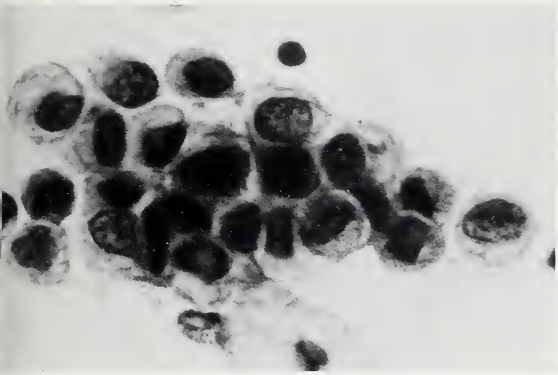

Fig. 124

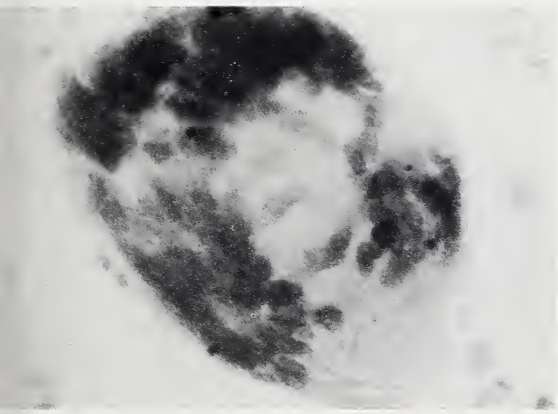

Fig. 125

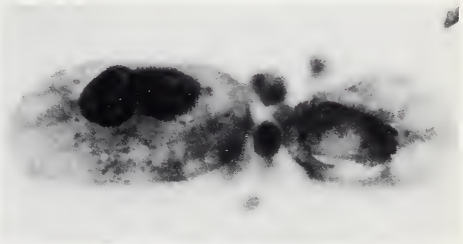

Fig. 126

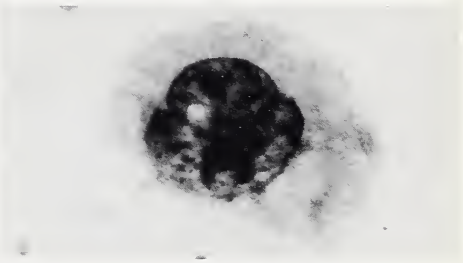

Fig. 127

Fig. 128

Fig. 129

Fig. 130

Fig. 131

Figure 132. Metaplastic squamous epithelium forming a syncytium. A. F. I. P. Acc. No. 218737–189.

Figure 133. Metaplastic squamous epithelium. The sharply outlined polygonal cells are smaller than normal squamous epithelium but possess relatively large nuclei. A. F. I. P. Acc. No. 218737–188.

Figure 134. A clump of vacuolated epithelial cells in sputum interpreted as metaplastic, rather than carcinomatous. Vacuolar change is often observed in metaplastic epithelium. A. F. I. P. Acc. No. 218737–190.

Figure 135. Cells from epidermoid carcinoma in sputum. This is a typical example of desquamated material from a well differentiated tumor. There is greater variation in size and shape of cells and nuclei than in the metaplastic epithelium, and nucleoli are larger. A. F. I. P. Acc. No. 218737–192.

Figure 136. Metaplastic squamous epithelium in sputum falsely interpreted as representing carcinoma. The patient had a lung abscess. × 743. (This is the same illustration as fig. 11 in Liebow, A. A., Lindskog, G. E., and Bloomer, W. E. Cytological studies of sputum and bronchial secretions in the diagnosis of cancer of the lung. Cancer, 1: 223–233, 1948.) A. F. I. P. Acc. No 218737–191.

Figure 137. Epithelial pearl from squamous cell carcinoma in sputum. (Compare with figure 131.) A. F. I. P. Acc. No. 218737–193.

Fig. 132

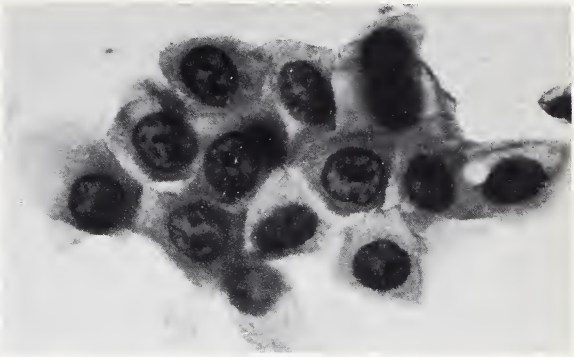

Fig. 133

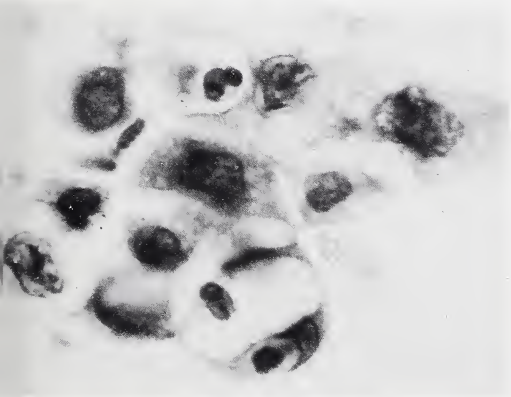

Fig. 134

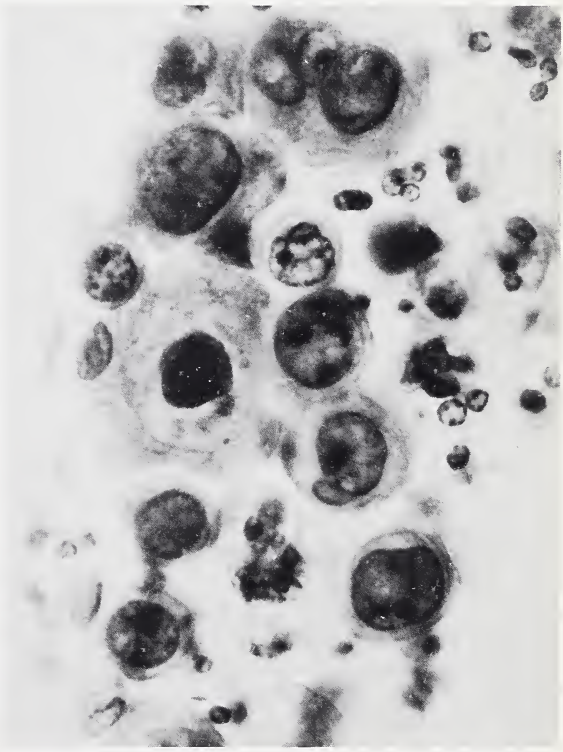

Fig. 135

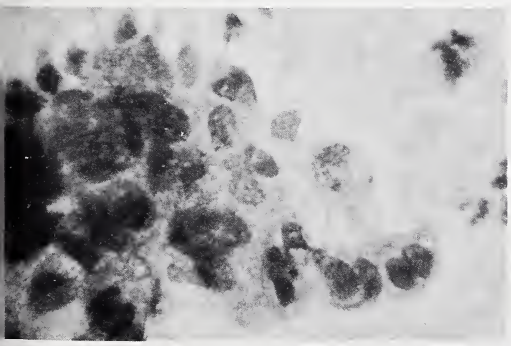

Fig. 136

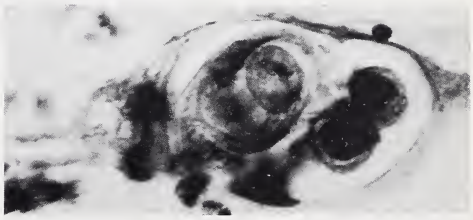

Fig. 137

CYTOLOGY OF SPUTUM IN NEOPLASTIC DISEASE OF LUNG

Figure 138.* Epidermoid carcinoma. Two of the cells are in mitosis. × 800, reduced about two-thirds. A. F. I. P. Acc. No. 218737–194.

Figure 139.* Anaplastic carcinoma. The cells in the berry-like cluster have extremely scanty cytoplasm and nuclei of variable size. The nucleoli are minute. This sputum specimen and the histologic section of the surgically resected tumor illustrated in figure 90 are from the same patient. × 800. A. F. I. P. Acc. No. 218737–195.

Figure 140. Higher magnification of cell group from same specimen as figure 141. A. F. I. P. Acc. No. 218737–197.

Figure 141. Columnar and berry-like masses of epithelium in sputum from patient with adenocarcinoma of lung. The berry-like clusters have also been observed in bronchiolar carcinoma. A. F. I. P. Acc. No. 218737–196.

Figure 142. Cells desquamated from adenocarcinoma in sputum. The vacuolated mucus-containing cytoplasm is suggestive of adenocarcinoma. A. F. I. P. Acc. No. 218737–198.

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*Reprinted from Liebow, A. A., Lindskog, G. E., and Bloomer, W. E. Cytological studies of sputum and bronchial secretions in the diagnosis of cancer of the lung. Cancer, 1: 223–233, 1948. Figures 5 and 6 are our figures 138 and 139.

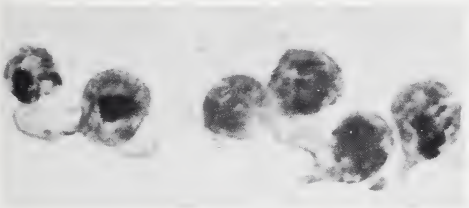

Fig. 138

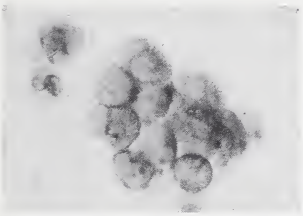

Fig. 139

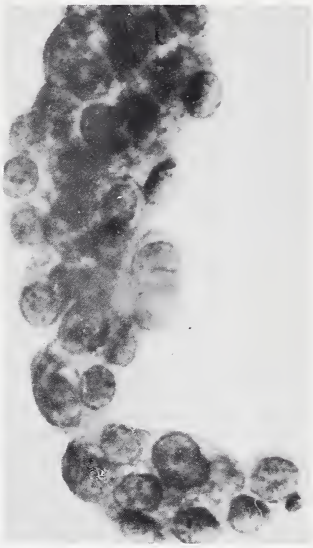

Fig. 140

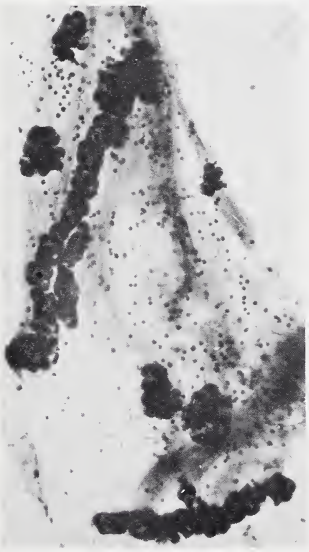

Fig. 141

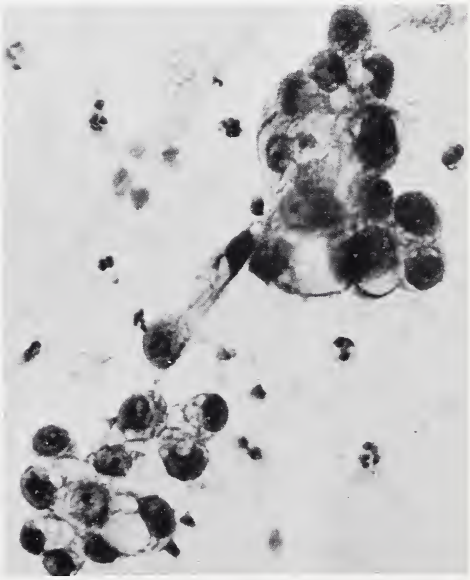

Fig. 142

CYTOLOGY OF SPUTUM IN NEOPLASTIC DISEASE OF LUNG

(Figures 143 and 144 are from the same case)

Figure 143. Loosely arranged group of cells with vaguely defined cell boundaries, desquamated from adenocarcinoma of lung. (This is the same illustration as figure 7 in Liebow, A. A., Lindskog, G. E., and Bloomer, W. E. Cytological studies of sputum and bronchial secretions in the diagnosis of cancer of the lung. Cancer, 1: 223–233, 1948.) A. F. I. P. Acc. No. 218737–199.

Figure 144. Cell in mitosis from another field of the same specimen illustrated in figure 143. A. F. I. P. Acc. No. 218737–200.

Figure 145. Very prominent multiple nucleoli in a cell group desquamated from adenocarcinoma of lung. A. F. I. P. Acc. No. 218737–201.

Figure 146. A large mass of cells with vacuolated cytoplasm and prominent nucleoli from the sputum of a patient with adenocarcinoma of the lung. A. F. I. P. Acc. No. 218737–203.

Figure 147. Group of vacuolated irregular cells in sputum from patient with adenocarcinoma of the lung. A suggestion of columnar form is retained. A. F. I. P. Acc. No. 218737–202.

Figure 148. A group of cells containing mucus desquamated from metastatic adenocarcinoma in the lung. The tumor is primary in the gastrointestinal tract. A. F. I. P. Acc. No. 218737–204.

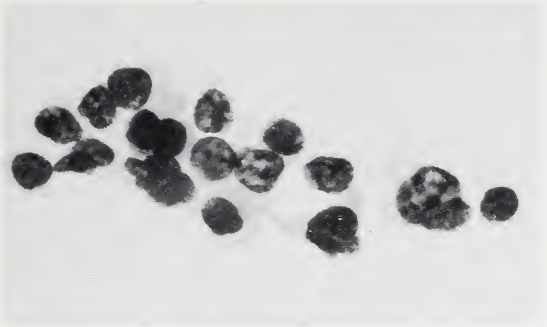

Fig. 143

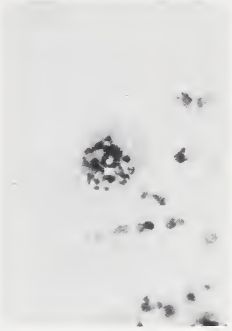

Fig. 144

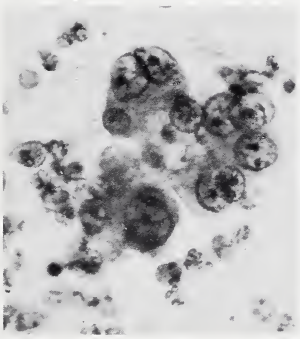

Fig. 145

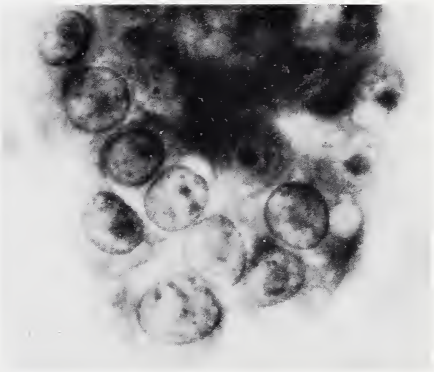

Fig. 146

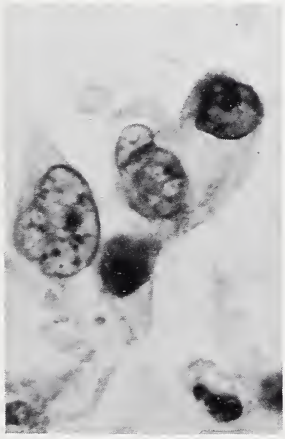

Fig. 147

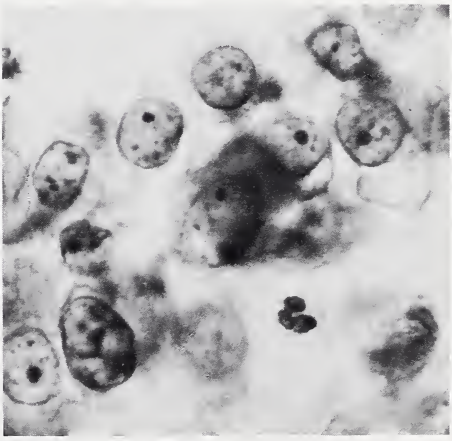

Fig. 148

Adenocarcinoma usually consists of cells of variable size with, frequently, mucin-containing foamy cytoplasm. Often these cells have irregular and indistinct outlines (figs. 142, 143, 147). The nuclei are finely reticular and possess a thin nuclear membrane. Nucleoli are often remarkable for their large size (fig. 145). Often they are multiple. These cells tend least to adhere to one another (figs. 142, 143, 147). Exceptionally, they do adhere in a remarkable tubular or columnar arrangement (figs. 141, 140).

Cells from mesodermal tumors may be found in the sputum, but extensive cytologic observations have not as yet been reported. In the case of lymphocytic sarcoma, neoplastic cells may appear in masses within the sputum, but distinction from cells of an exudate is difficult (fig. 180).

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MESODERMAL TUMORS OF BRONCHI AND LUNGS

Tumors composed of connective tissue or its more differentiated derivatives may occur in pure or mixed form. Histologically benign and malignant forms of mesodermal neoplasms occur, and each may be subdivided into three groups: the tumors of vascular origin, the intrabronchial lesions which involve the segmental and more proximal bronchi, and the peripherally situated tumors that have their origin in the terminal parts of the respiratory tree. Mesodermal tumors of intermediate bronchi are rare.

BENIGN VASCULAR TUMORS

The status of vascular lesions as true neoplasms is very much in doubt. The cavernous vascular lesions have the least standing as new growths but are discussed in this fascicle in greater detail than the other forms of vascular tumors, as there are special characteristics exhibited by these lesions in this location.

Cavernous Vascular Lesions

SYNONYMS AND RELATED TERMS: Arteriovenous fistula; hemangioma; telangiectasis.

The cavernous vascular lesions are communicating large dilated tortuous vascular channels with both venous and arterial connections. Some class them as hamartomas, but they lack the organoid structure exhibited by the relatively common solid parenchymal tumors described below. A congenital factor

in their genesis is indicated by the evident presence of some at birth, and by the association of at least one in four with more general manifestations of the hereditary hemorrhagic telangiectasis (Rendu-Osler-Weber disease).

NATURAL HISTORY. Whatever their origin, these lesions have in common large channels of communication between pulmonary arteries and veins, which account for the characteristic manifestations of the condition. The clinical manifestations may not appear until early adult life. It is not known to what extent the lesions may change over a period of years. Some appear to remain static in adult life (figs. 149, 151). Among the signs and symptoms are most commonly cyanosis, clubbing of the fingers, extracardiac bruit, and dyspnea. There are usually polycythemia and desaturation of the peripheral arterial blood. The shadows in the roentgenogram often appear as single or multiple convoluted lobular bands connected with the hilum. Their size is decreased by the Valsalva, and increased by the Mueller maneuver (figs. 151, 150). Diagnostic pneumothorax, body section radiography, and especially angiocardiography are helpful. The latter have their limitations in the case of superficial lesions and are attended with some danger on account of concomitant polycythemia. Complications are chiefly those of cerebral thrombosis associated with polycythemia. Alarming or fatal hemorrhage may occur into the lung or pleural cavity. Infection is possible with a result analogous to that of bacterial endocarditis. In contrast with peripheral arteriovenous fistulas, the cardiac output is usually normal and the hypervolemia is chiefly the result of increase in the volume of the red cell mass. There is usually no evidence of cor pulmonale.

GROSS. The lesions are usually multiple. The right lower and middle lobes are most commonly involved, the latter in striking disproportion to its relative volume. In some instances, the atypical vessels lie deep in the parenchyma. Sometimes, however, one or more are visible at the pleura where they may even present as pedunculated vesicles resembling emphysematous blebs, but filled with blood (figs. 152, 153). In those few instances where a careful dissection or injection is available, one or more major arteries or veins are involved, but there is no constancy in the pattern (figs. 152–155). During surgical dissections, the walls of the vessels have in some instances been described as thin and friable, making extreme care in dissection necessary.

MICROSCOPIC. There is variation in the structure of the walls of the cavernous channels. Most have thin walls with a minimum of muscle and consist almost entirely of endothelium supported by an extremely thin connective tissue lamina. Others are provided in places with thick irregular muscular cushions (figs. 156, 157). Whatever the structure, venous components are no longer histologically distinguishable from the arterial.

Capillary Hemangiomas and Endotheliomas

These tumors are rare in the lungs and when they occur have the characteristics of similar tumors elsewhere. Plant presents two cases with review of

CAVERNOUS VASCULAR LESIONS

(Figures 149–153 are from the same case *)

Figure 149. Angiocardiogram made eight years preoperatively in a patient with cavernous hemangioma of lung. Broad bandlike shadows extend to the apex of the left lung. There were no symptoms or significant desaturation of the systemic arterial blood. A. F. I. P. Acc. No. 218737–205.

Figure 150. Roentgenogram during Mueller maneuver. The vascular shadow is larger in comparison with figure 151. There has been no significant change in eight years. (Compare with figure 149.) A. F. I. P. Acc. No. 218737–206.

Figure 151. Roentgenogram during Valsalva maneuver showing decrease in vascular shadow. A. F. I. P. Acc. No. 218737–207.

Figure 152. Diagram showing relations of the vessels involved in the hemangioma. There is a sac that protruded in the manner of a blood-filled bleb at the apex of the lung. It was supplied by two apical segmental arteries (A'a and A'b) and drained by a single large vein (V'a). A. F. I. P. Acc. No. 218737–208.

Figure 153. Vinylite bronchovascular cast corresponding to the diagram in figure 152. The bronchial tree (white) is also shown. Its branches ramify through the interstices of the vascular complex, without distortion or bronchiectasis. A. F. I. P. Acc. No. 218737–209.

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*Reported by Lindskog, G. E., Liebow, A. A., Kausel, H., and Janzen, A. Pulmonary arteriovenous aneurysm. Ann. Surg., 132: 591–606, 1950. Figures 1A, 1B, 1C, 2B, and 2A are our figures 149–153 respectively.

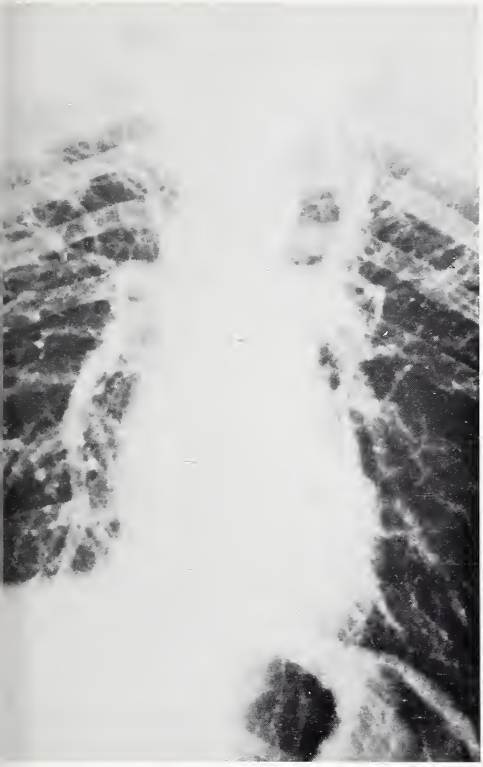

Fig. 149

Fig. 150

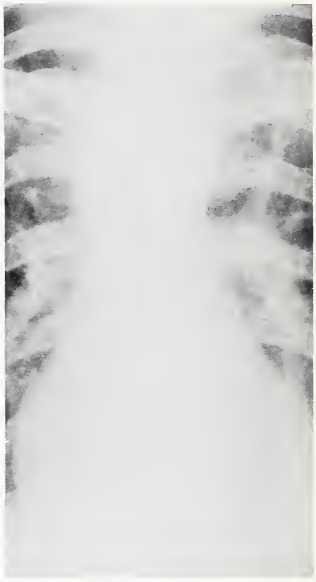

Fig. 151

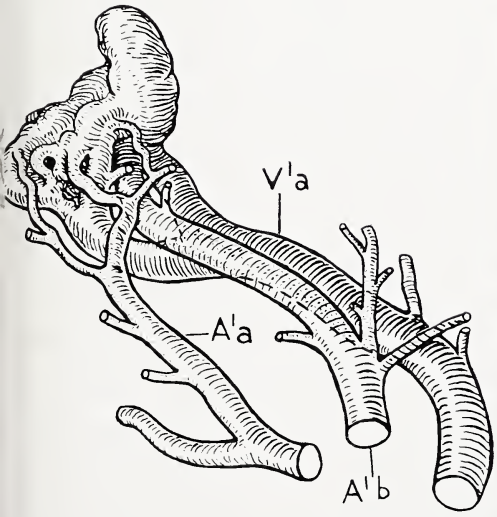

Fig. 152

Fig. 153

CAVERNOUS VASCULAR LESIONS

(Figures 154–157 are from the same case*)

Figure 154.* Diagram of essential structures involved in a cavernous hemangioma of the right lower lobe. Two separate vascular loops are shown. A. F. I. P. Acc. No. 218737–210.

Figure 155.* Vinylite bronchovascular cast of the specimen in figure 154. A. F. I. P. Acc. No. 218737–211.

Figure 156. Histologic section of cavernous hemangioma of lung encountered as an incidental finding at necropsy. There is great variation in the thickness of the walls of the vascular channels. Arterial and venous components cannot be distinguished with certainty. × 7. A. F. I. P. Acc. No. 218737–61.

Figure 157. Detail of figure 156 showing abundance of smooth muscle in a particular vascular segment. × 150. A. F. I. P. Acc. No. 218737–39.

Figure 158.* Vinylite bronchovascular cast of another hemangioma of the lung. A bronchial artery, injected in black plastic, can be seen to ramify upon the wall of the large sac, in the manner of vasa vasorum, but it is not involved in the angiomatous complex. A. F. I. P. Acc. No. 218737–212.

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*Reprinted from Lindskog, G. E., Liebow, A. A., Kausel, H., Janzen, A. Pulmonary arteriovenous aneurysm. Ann. Surg., 132: 591–606, 1950. Figures 4B, 4A, and 6C are our figures 154, 155, and 158 respectively.

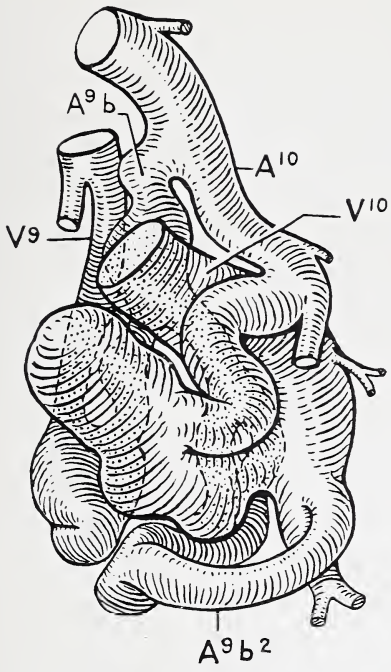


Fig. 154

Fig. 155

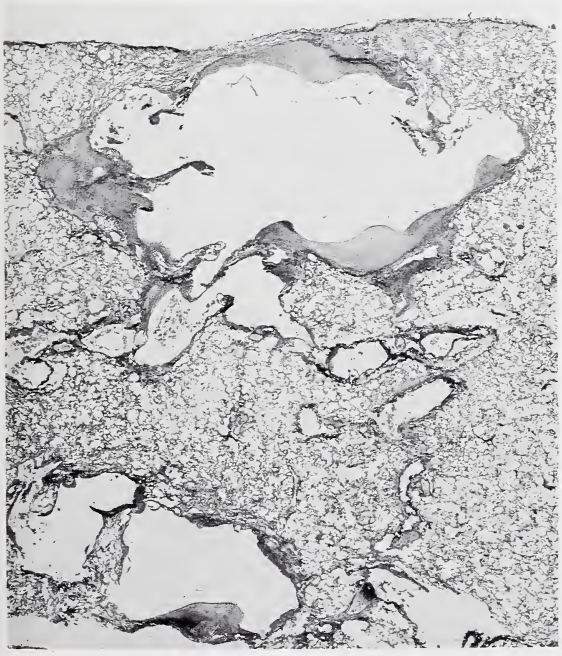


Fig. 156

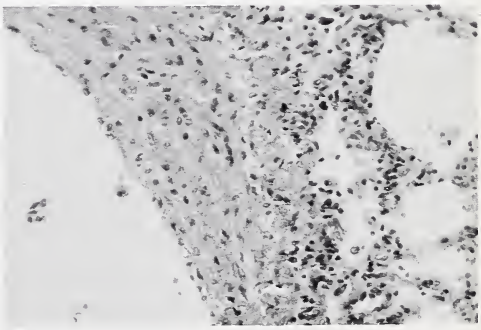


Fig. 157

Fig. 158

the literature. (See also Fascicle 5, "Tumors of the Soft Tissues," and Fascicle 7, "Tumors of the Cardiovascular System.")

MALIGNANT VASCULAR TUMORS

Malignant tumors of the vessels may exist, but in two reported instances (Hall, Wollstein), the presence of tumors elsewhere makes the lung uncertain as a primary source.

A remarkable instance of a chondrosarcoma that appeared to be limited to the pulmonary artery and its branches without discontinuous metastases has been described by Lowell and Tuhy.

BENIGN INTRABRONCHIAL* TUMORS

The benign intrabronchial tumors, despite their diversity of histologic structure, have many features in common, and they will first be discussed in general terms. More specific consideration will be given to the more common types. These tumors are almost always situated in the main bronchi. Fibromas and chondromas together account for between 80 and 90 percent of all lesions of this type, and the former are somewhat the more numerous (Bartlett and Adams). Leiomyomas, lipomas, lymphomas, a myoblastoma, and a plasmocytoma have also been described, as have tumors exhibiting an admixture of various mesodermal tissues. Infoldings of epithelium may exist at the surface but are not an integral part of the neoplasm, as they are in hamartoma.

The symptoms in the main resemble those of adenoma and are likewise often of very long duration. Hemorrhage is not as common as it is in adenoma, but may come from the associated bronchiectatic sacs.

The age at time of treatment varies widely but averages approximately 10 years less than that of carcinoma. Men are involved three times as frequently as women.

The tumors occur in almost equal incidence in the two lungs. The benign intrabronchial mesodermal tumors usually are truly pedunculated in contrast with the bronchial adenomas. In a few cases, however, there is penetration of the outer coats of the bronchus so that an encapsulated tumor mass, which projects into the bronchus, also presents a large surface to the pulmonary parenchyma or mediastinum. The pedicle varies in length, and even when the tumor is quite sessile the point of attachment is narrower than the free end, which is usually directed proximally (fig. 159).

Fibroma

These tumors vary in structure. Some consist of closely packed spindle-shaped cells, others contain more collagen, or are myxomatous, and some contain various amounts of adipose tissue. Ossifying fibromas have been described. Cystic changes may occur. The relatively frequent "inflammatory polyps," prolapsed masses of edematous mucous membrane often con-

*Includes the main carina.

taining granulation tissue resulting from infection, have occasionally been confused with the true neoplasms.

Chondroma and Osteochondroma (figs. 159–163)

Chondromas are very firm and have a blue-white translucency when composed of hyaline cartilage. They are more opaque and yellow-white when there is abundant fibrous or elastic tissue. Hyaline cartilage, fibrocartilage, elastic cartilage, or combinations may exist. The cartilage contains abundant glycogen, may contain red-tan or dull yellow fragments of ossified or calcified material, and may be accompanied by myxomatous connective tissue and fat.

The relation of the chondromas to the so-called hamartomas has been questioned. They differ not only in position but also in microscopic structure. The chondroma of the major bronchi consists of purely mesodermal tissue. Although there may be some infolding and epithelial-lined cystic spaces, probably representing dilated glands or ducts that have been trapped within the growing neoplasm, there is not the intimate admixture of proliferating epithelium and diverse elements of connective tissue that characterize the hamartomas. Some of the chondromas appear to be true ecchondroses of the bronchial cartilages, but others possess their own capsules. Rarely, tumors of hamartomatous structure have been found in the major bronchi.

Lipoma

Fatty tumors are third in incidence. Fat is always present in the larger bronchi, usually externally to the cartilages. There is often also an admixture of adipose tissue in mesodermal tumors in which other connective tissue elements are dominant. The essential gross features resemble those of other benign intrabronchial tumors (figs. 173–175).

Granular Cell Myoblastoma

A rare instance of polypoid granular cell myoblastoma of the bronchus is illustrated in figures 164 and 165. Up to 1949 Murphy, Dockerty, and Broders found reference to three tumors of this type in the trachea or bronchi. These constituted 1.3 percent of the 229 myoblastomas surveyed.

The histogenesis of these tumors in sites where striated muscle does not normally exist is uncertain, although several theories have been proposed: that they are derived from totipotential mesenchyme differentiating into striated muscle; that they are composed of histiocytes and represent a type of local "storage disease," analogous to xanthoma; and that they are a form of neurofibroma.

MALIGNANT INTRABRONCHIAL TUMORS

Gradually the old view that sarcomas of the lung are common has been abandoned, and most "oat-cell," "round-cell," or "spindle-cell" tumors are now recognized as being composed of undifferentiated epithelium.

CHONDROMA OF BRONCHUS

(Figures 159–162 are from the same case)

Figure 159. A firm pedunculated mass obstructs the anterior basal bronchus of the right lower lobe. Its expanded head projects proximally. A. F. I. P. Acc. No. 218737–9.

Figure 160. Longitudinal section through the narrow pedicle in the direction of the anterior basal bronchus. The cut surface has the appearance of cartilage. A. F. I. P. Acc. No. 218737–24.

Figure 161. Histologic section corresponding to figure 160. The epithelium of the surface does not take part in the formation of the neoplasm. × 9. A. F. I. P. Acc. No. 218737–63.

Figure 162. Higher power of a portion of the histologic slide shown in figure 161. There is abundant loose fibrous stroma among the islands of cartilage. The surface is covered by an intact pseudostratified ciliated columnar epithelium. A. F. I. P. Acc. No. 218737–213.

Fig. 159

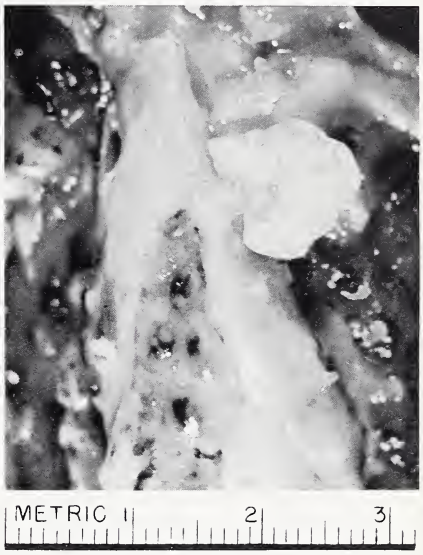


Fig. 160

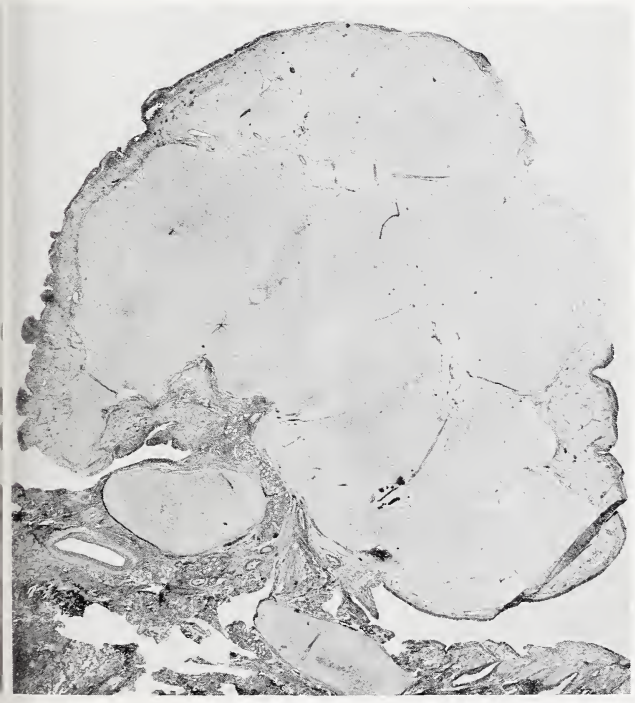


Fig. 161

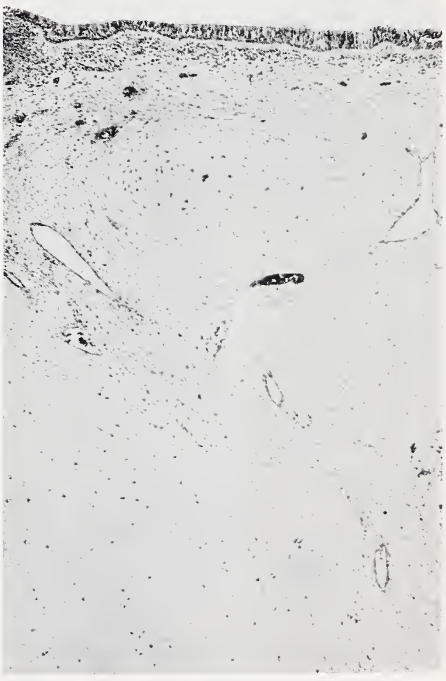


Fig. 162

BENIGN INTRABRONCHIAL MESODERMAL TUMORS

(Figures 164 and 165 are from the same case)

Figure 163. Osteochondroma of bronchus. × 75. (From the Armed Forces Institute of Pathology.) A. F. I. P. Acc. No. 73536–2.

Figure 164. Granular cell myoblastoma. This polypoid mass, measuring 3 x 4 x 5 mm., projected into the main bronchus of the left upper lobe of a 59-year-old negro male. There is squamous metaplasia of the bronchial epithelium covering and adjacent to the mass. Acanthotic projections of the squamous epithelium extend into the depths of the tumor, as is common in the similar lesions of the tongue. (From the Armed Forces Institute of Pathology.) A. F. I. P. Acc. No. 284700–24041.

Figure 165. Higher magnification of figure 164 demonstrating the pyknotic nuclei and granular cytoplasm of the component cells of the tumor and the focal acanthosis of the covering squamous epithelium. A thin layer of connective tissue separates the tumor cells from the epithelium. × 145. (From the Armed Forces Institute of Pathology.) A. F. I. P. Acc. No. 284700–24042.

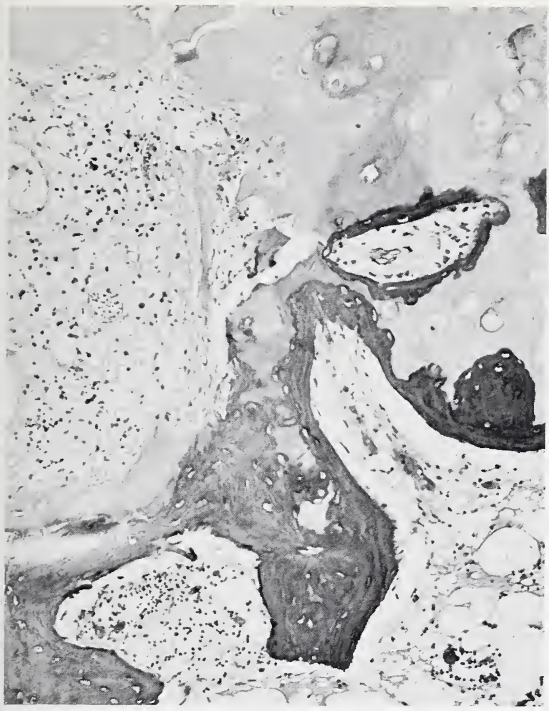


Fig. 163

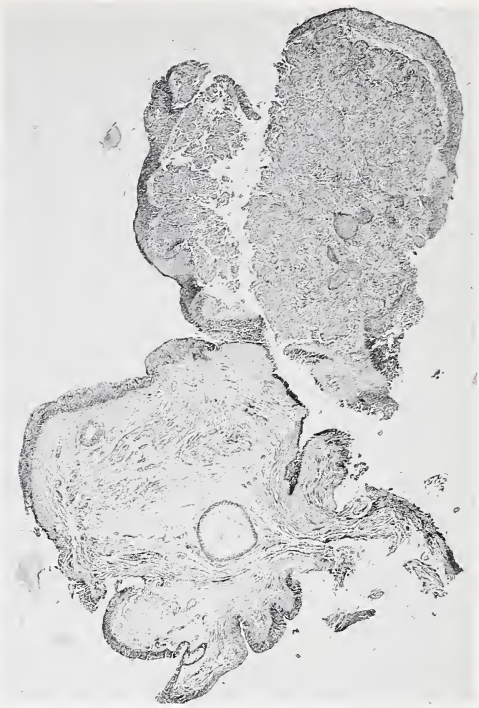


Fig. 164

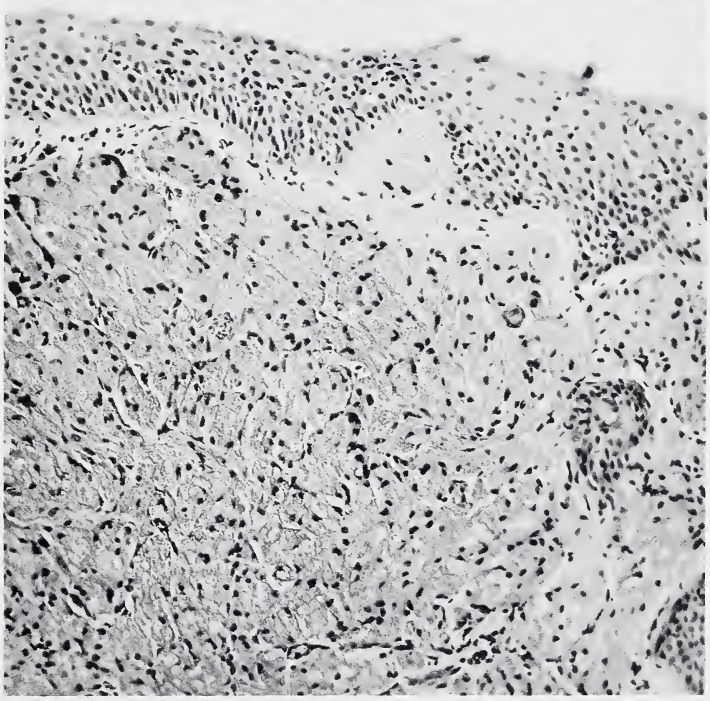


Fig. 165

OSTEOCHONDROMATOSIS

(Figures 166–172 and plate III–B are from the same case)

Figure 166. Lateral roentgenogram showing ovoid mass with spicular calcific densities. This was an asymptomatic lesion in a 55-year-old woman that was discovered in a routine survey photoroentgenogram. She had had "pneumonia" 12 years previously from which she had completely recovered. A lesion was described in the right lower lobe at the time of this illness as "mottled, irregular densities." Unfortunately, it was not possible to review these earlier films for comparison with figure 166. A. F. I. P. Acc. No. 218737–297.

Figure 167. Lateral aspect of resected right lower lobe showing irregular protrusions of bony consistency elevating the pleura in the region of the lateral and anterior basal segments. The cut surface of this lesion is shown in plate III–B. A. F. I. P. Acc. No. 218737–298.

Figure 168. Roentgenogram of the surgically removed specimen showing spicular calcific densities. A. F. I. P. Acc. No. 218737–300.

Figure 169. In the lower left-hand corner of the photograph a small bronchus is shown. There are plates of bone in the connective tissue immediately beneath the epithelium. Externally, there are very large masses of cartilage that become continuous with thin trabeculae of bone at the right. Among the latter, there is adipose tissue. A. F. I. P. Acc. No. 218737–303.

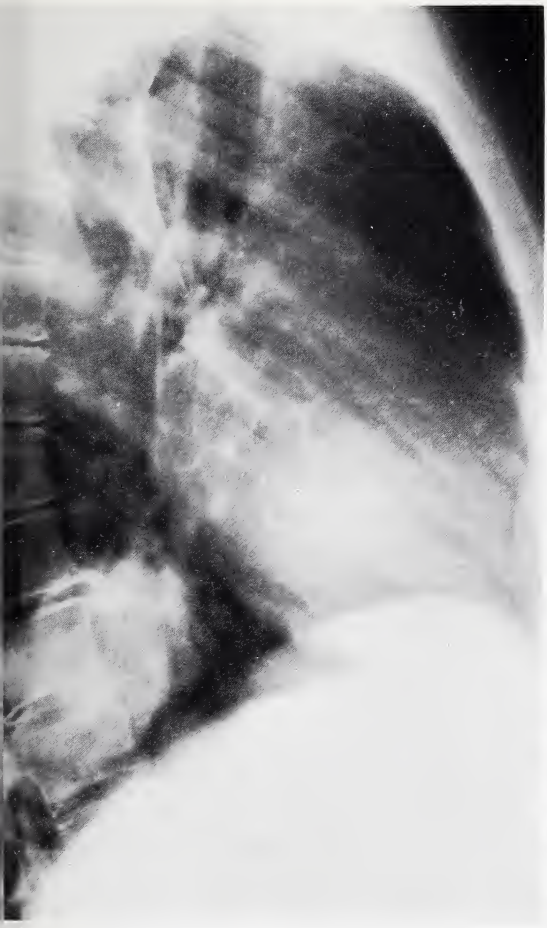


Fig. 166

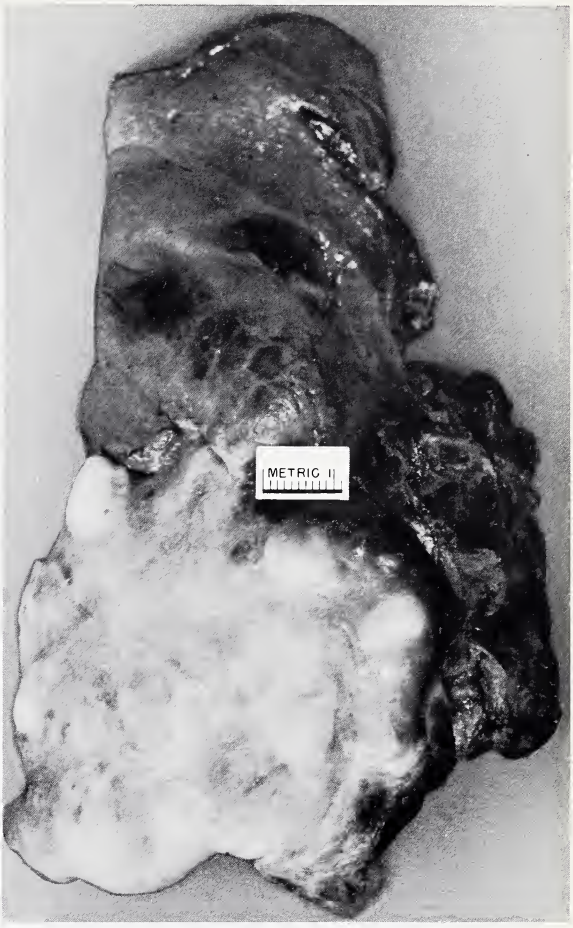


Fig. 167

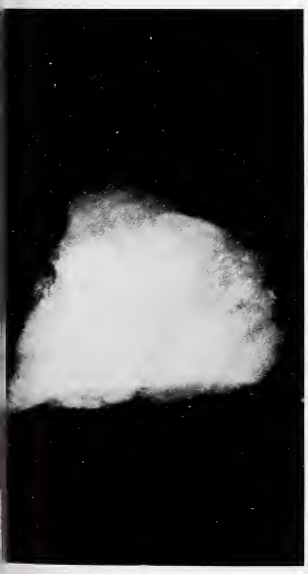


Fig. 168

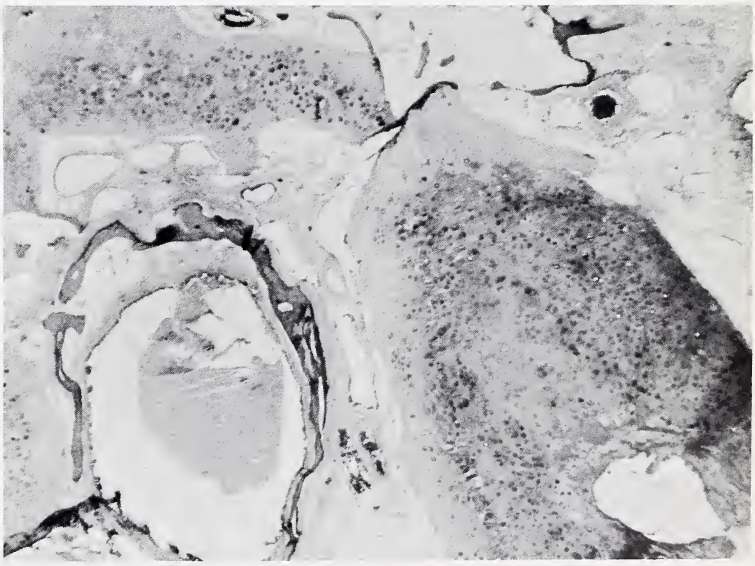


Fig. 169

OSTEOCHONDROMATOSIS

(Figures 166–172 and plate III–B are from the same case)

Figure 170. The wall of a bronchus is shown. The ciliated epithelium is intact. Beneath it, there are two spicules of bone continuous with a huge mass of hyaline cartilage. A. F. I. P. Acc. No. 218737–305.

Figure 171. Several large masses of bone containing fatty tissue are shown. Some of the trabeculae become continuous with rounded masses of hyaline cartilage. A. F. I. P. Acc. No. 218737–304.

Figure 172. In this field, there is a cellular marrow containing both leucopoietic and erythropoietic tissue among the spicules of bone. This tissue was also related to the wall of the bronchus as in figure 170. A. F. I. P. Acc. No. 218737–306.

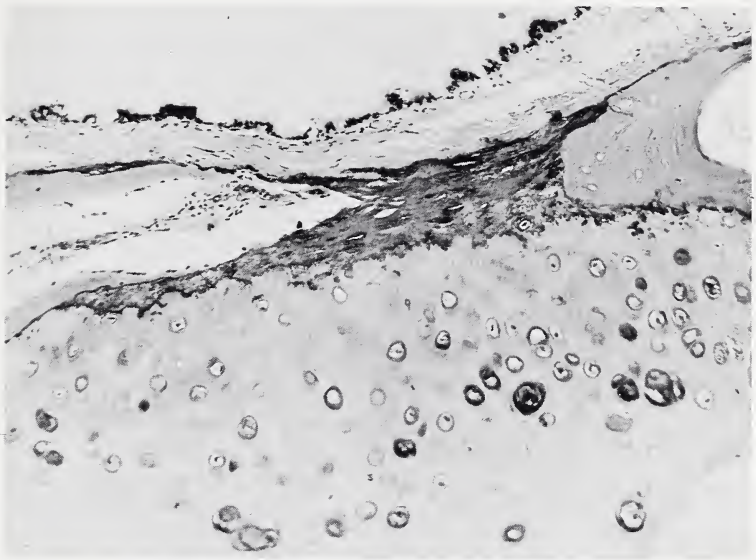


Fig. 170

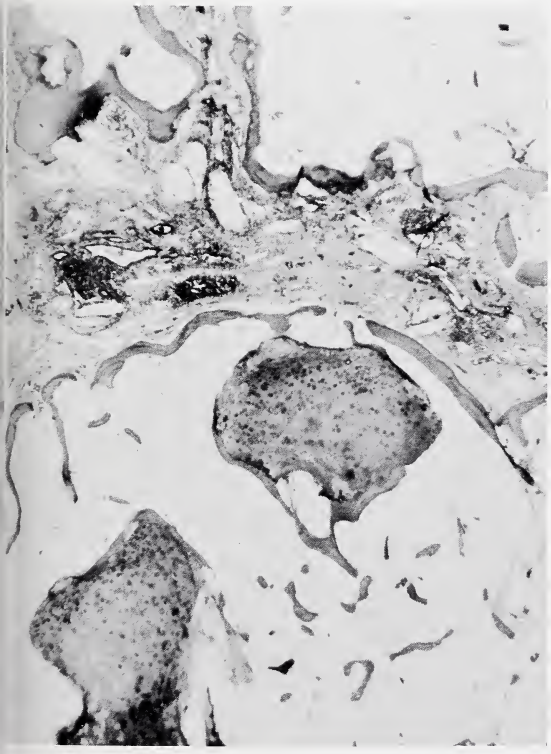


Fig. 171

Fig. 172

LIPOMA OF THE BRONCHUS

(Figures 173–175 are from the same case*)

Figure 173. Lipoma of upper lobe stem bronchus. This was a soft pedunculated mass. A. F. I. P. Acc. No. 138325–3.

Figure 174. Histologic section through the stalk of the tumor shown in figure 173. The main mass is attached along the carina, a cartilage of which is within the narrow pedicle. The latter has been fractured and displaced in the preparation. The main mass consists of adipose tissue. There is some infolding of the epithelium at the surface. × 7. A. F. I. P. Acc. No. 138325–1.

Figure 175. Detail of figure 174. Intact pseudostratified columnar epithelium covers the surface of the lipoma. × 45. A. F. I. P. Acc. No. 138325–2.

*From the Armed Forces Institute of Pathology.

Fig. 173

Fig. 174

Fig. 175

LEIOMYOSARCOMA OF BRONCHUS

(Figures 176–179 are from the same case*)

Figure 176. Lateral roentgenogram of the thorax of a 34-year-old negro male. Symptoms were chronic cough, dyspnea, and weakness beginning with persistent cough two years before an illness diagnosed as "pneumonia, right lung." There had been one episode of hemoptysis. A chest X-ray at the time of "pneumonia" revealed a tumor and associated atelectasis in the right lung. During bronchoscopy a smooth, rounded tumor mass was seen occluding the right main bronchus and partially covering the carina. Following repeated bronchoscopic resections of the tumor the right lung partially re-expanded but the patient began to have hemoptyses in amounts up to 400 cc. Five months after the tumor was first demonstrated a right pneumonectomy was attempted but the patient died during the operation from a massive hemorrhage into the left main bronchus. A. F. I. P. Acc. No. 166844–2.

Figure 177. Anteroposterior roentgenogram showing radiopaque mass in right upper lobe. Compare with figure 178. A. F. I. P. Acc. No. 166844–1.

Figure 178. One tumor mass is seen attached to the carina and a second projects into the right main bronchus and infiltrates into the surrounding lung. The tumor in both places was soft, friable, and hemorrhagic. Aspirated blood fills the left bronchial tree. No metastases were found. A. F. I. P. Acc. No. 166844–6.

Figure 179. Histologic section of tumor illustrated in figure 178. × 545. A. F. I. P. Acc. No. 166844–11.

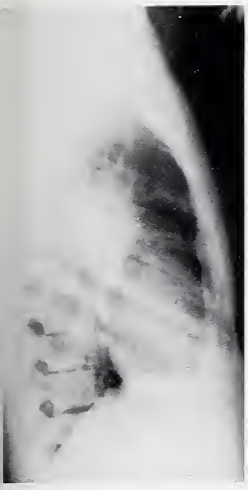


Fig. 176

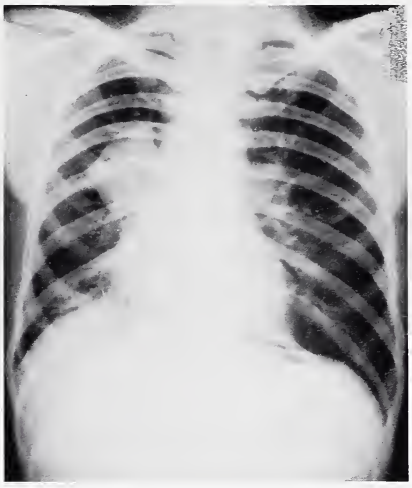


Fig. 177

Fig. 178

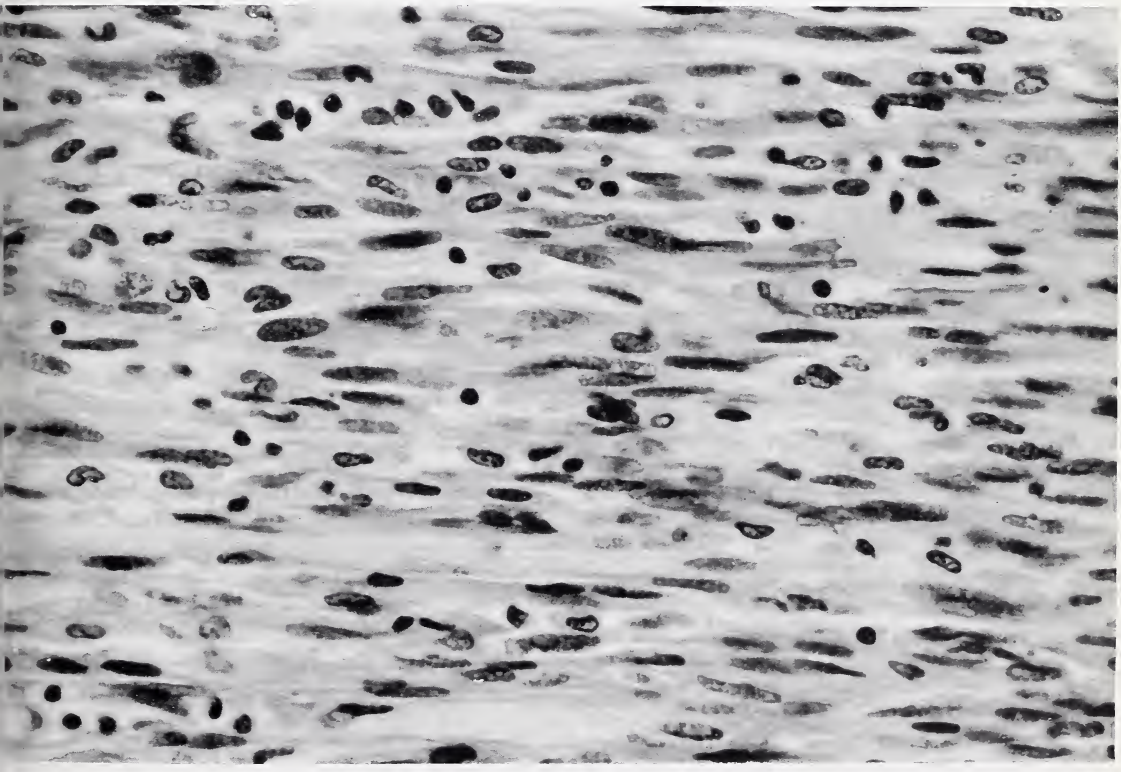


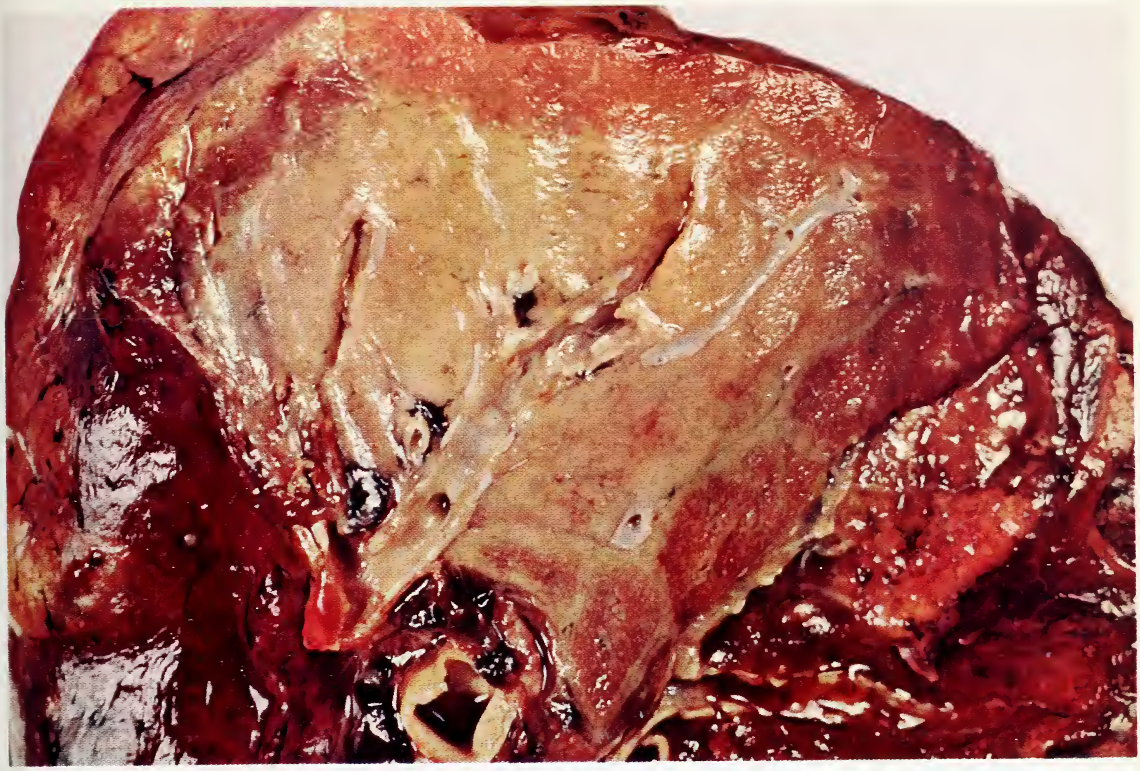
Fig. 179

PLATE III

A. Primary lymphosarcoma of the lung, apical segment of left upper lobe. The fleshy firm pale yellow tumor had a greatest dimension of 6 to 7 cm. Histologic section of the tumor is illustrated in figure 181. No tumor was found in the eleven regional lymph nodes examined. The patient, a 75-year-old female, had a history of an upper respiratory tract infection for six months before pneumonectomy. A slight restriction of the left main stem bronchus in its lateral motion was seen by the bronchoscopist. Malignant cells were found in the sputum (see fig. 180). (Case presented through the courtesy of Dr. Lauren V. Ackerman. This figure in black and white is figure 10 from Jackson, E., Bertoli, F., and Ackerman, L. V. Exfoliative cytology. J. Thoracic Surg., 21: 7–23, 1951.) A. F. I. P. Acc. No. 218737–263.

B. "Osteochondromatosis." Coronal section of right lower lobe at a level approximately 4 cm. above the diaphragmatic surface. The anterior and lateral basal bronchi are rigid structures. There are ossification and proliferation of cartilage in their walls. Distally, the parenchyma resembles the cut surface of cancellous bone. It contains irregular islands of blue-white cartilaginous translucency and consistency. A dull red marrow-like substance exudes from spaces among the spicules of bone, while elsewhere there is yellow adipose tissue within the framework of bone. (See also figures 166–172 from the same case.) A. F. I. P. Acc. No. 218737–299.

C. Mesothelioma of the pleura. Autopsy specimen of left lung, pleuropericardial lamina, and the diaphragm. The visceral and parietal pleura are both greatly thickened by a diffuse tumor. The left lung has been compressed against the mediastinum as a result of massive accumulation of serosanguineous fluid. A complete necropsy revealed neither metastases nor a primary tumor elsewhere. (See figures 232–236 from the same case.) A. F. I. P. Acc. No. 218737–237.



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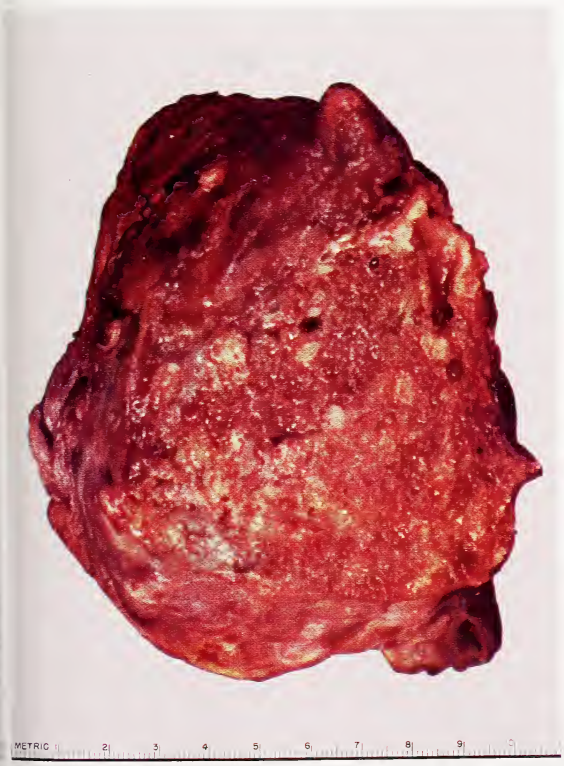

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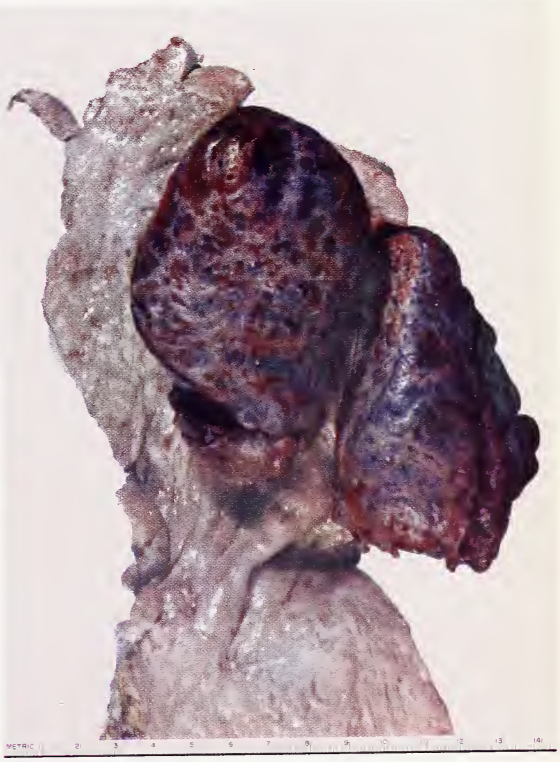

C

PLATE III

LYMPHOSARCOMA OF THE LUNG

(Figures 180 and 181 and plate III–A are from the same case)

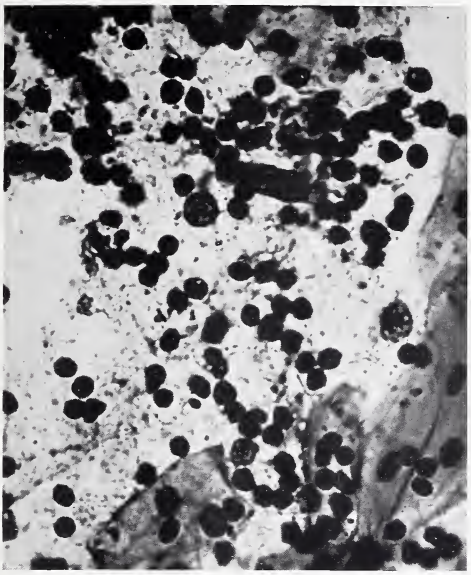

Fig. 180

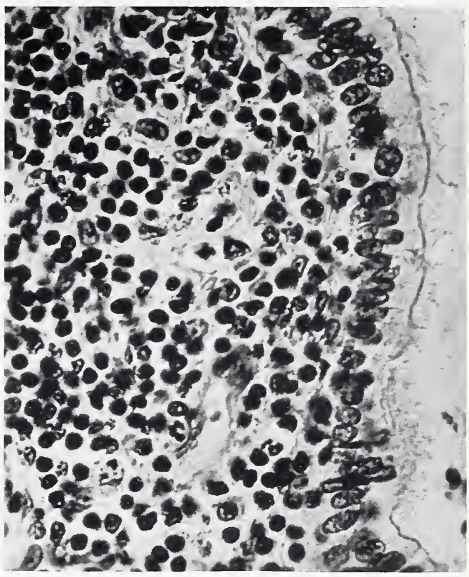

Fig. 181

Figure 180.* Smear of sputum showing groups of pyknotic nuclei of lymphocytes from a patient with lymphosarcoma of the lung. The gross specimen of the tumor is illustrated in plate III–A. A. F. I. P. Acc. No. 218737–265.

Figure 181.* Histologic section from gross specimen illustrated in plate III–A. Lymphocytes of almost uniformly small size infiltrate the lamina propria. These extend as a consolidating mass into the surrounding parenchyma. There is no necrosis or destruction of the epithelium of the bronchus. A. F. I. P. Acc. No. 218737–264.

*Case presented through the courtesy of Dr. Lauren V. Ackerman, Barnes Hospital, St. Louis, Missouri. Reported by Jackson, E., Bertoli, F., Ackerman, L. V. Exfoliative cytology. J. Thoracic Surg., 21: 7–23, 1951. Figs. 11 and 12 are our figs. 180 and 181.

These tumors occur even more rarely than the benign variants. So few have been reported that it is not possible to make more than general statements concerning their characteristics. Clinically, they tend to occur even earlier in life than the benign variants. They appear most frequently in the second and third decades. The symptoms are very similar to those of the pulmonary adenoma . Again, hemorrhage may be a prominent symptom. Most of these malignant polypoid tumors have been described as relatively soft and hemorrhagic, with a tendency to penetrate beyond the boundaries of the bronchus of origin into the surrounding parenchyma. The main stem bronchi are almost always involved.

Fibrosarcoma

Fibrosarcomas are the most common tumors of this group, although less than 12 authentic instances have been reported to 1950. Some do not possess the clinical malignancy suggested by their histologic appearance.

Osteochondrosarcoma

An osteochondrosarcoma has been reported by Greenspan, which involved the left main bronchus and extended into the adjoining lung and mediastinum as well as into the pulmonary artery and surface of the heart.

Leiomyosarcoma

The tumor reported as a leiomyosarcoma by Randall and Blades is illustrated in figures 176 to 179.

BENIGN PARENCHYMAL TUMORS

It may be difficult to state whether a peripheral connective tissue tumor not obviously associated with a bronchus has originated in the parenchyma itself, the pleura, or a minute bronchus. The elastic tissue delimiting the pleura may serve as a guide, but it is often destroyed or surrounded by neoplastic tissue of whatever origin. Most connective tissue tumors of the parenchyma appear to be leiomyomatous and occur chiefly in women. The question arises as to whether some may not in fact represent metastases from smooth muscle tumors of the uterus as described by Steiner. A peripheral neurogenic tumor has recently been described by Bartlett and Adams.

A rare instance of what can best be described as "osteochondromatosis" is illustrated in figures 166–172. In this lesion the cartilages of many bronchi in the anterior and lateral basal segments have been transformed into masses of well differentiated proliferating cartilaginous and osseous tissue with adipose or cellular marrow. The process appears to be essentially one of metaplasia, but with a striking degree of proliferation. The lesion lacks the sharp delimitation of a hamartoma, and the large cartilages of the main anterior and lateral segmental bronchi of the lower lobe have been transformed in a manner similar to that of their branches in the parenchyma.

MALIGNANT PARENCHYMAL TUMORS

Well established malignant primary connective tissue tumors arising in the extrabronchial connective tissue of the lung are among the greatest of rarities. In making a search for reports of such tumors, multiple lesions and those in which the ribs are involved should be considered extremely dubious. The evaluation of published material is rendered additionally difficult for lack of illustrations.

A few apparently authentic cases that have been described have little in common in the way of symptoms until they have reached a very large size, at which time pain in the chest, dyspnea, and even cyanosis may become prominent. Despite their enormous size and the malignant histologic appearance, these tumors do not appear to metastasize widely.

These lesions are usually stated to be soft, friable, and hemorrhagic. Spindle cell sarcomas have been described by Ball and by Pritchard. The former demonstrated an extremely rich network of reticulin fibers that embrace the individual cells. Figures 182 to 186 illustrate a tumor tentatively interpreted as a liposarcoma.

A group of massive "sarcomas" has been described in children less than 15 years of age. Most of these reports are not illustrated, and necropsy reports are incomplete, or lacking entirely. Until more accurate studies are available, decision concerning the nature of these tumors must be held in abeyance.

Lymphosarcoma

Reports are accumulating of cases of lymphosarcoma that give many indications of originating within, and remaining confined to the lung. Similar to one another in their gross and microscopic features are the instances reported by Churchill, Maier, and by Anlyan, Lovingood, and Klassen, and the specimen illustrated in figures 180, 181, and plate III–A. The lesion was asymptomatic and discovered by roentgenography in two of these patients. There were, however, signs indicating pulmonary consolidation. The ages of the patients ranged from 45 to 63 years. In the 63-year-old man reported by Anlyan, Lovingwood, and Klassen, there was no evidence of change in the shadow in the lung field in an interval of six months. In the case reported by Maier a shadow appeared in the right lung field one and one-half years after left pneumonectomy for the original lesion, but the presumed recurrence seemed to melt away after roentgen therapy without returning in the subsequent 18 months.

GROSS. The neoplastic tissue is translucent, pale grey-pink, and merges imperceptibly with the surrounding parenchyma without interposition of a capsule. Indeed, in the specimen described by Maier, the tumor had passed across the obliterated fissure between the left upper and lower lobes. In the others it was confined to a single lobe. In none was there evidence of involvement of the lymph nodes at the hilum or elsewhere.

MICROSCOPIC. The tumor has the structure of lymphocytic lymphosarcoma. There is no evidence of necrosis. At the margins of the lesion, there

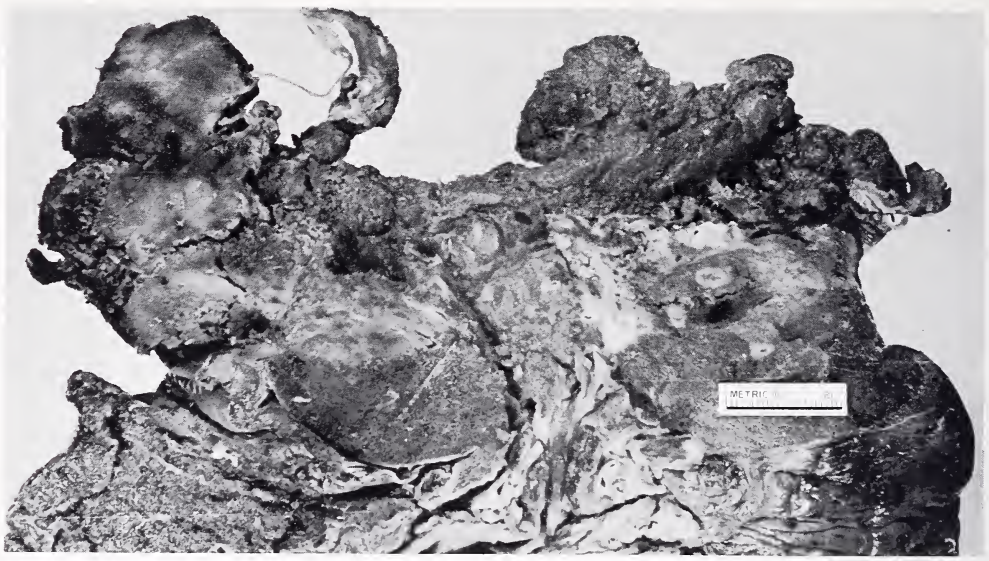

Fig. 182

POSSIBLE LIPOSARCOMA OF LUNG

(Figures 182–186 are from the same case)

Figure 182. Tumor interpreted as a liposarcoma of the lung. An enormous poorly demarcated hemorrhagic mass involves most of the left upper lobe. The tumor was very friable and it was not possible to avoid tearing its substance during left pneumonectomy. No metastases were found in the peribronchial lymph nodes. A. F. I. P. Acc. No. 218737–214.

Figure 183. Histologic section of the tumor illustrated in figure 182. While the tissue resembles somewhat the atypical portions of the epidermoid carcinoma shown in figures 84–86, it is even more pleomorphic and infiltrative. Spindle-shaped cells of variable size predominate but giant cells are numerous. Neoplastic cells infiltrate the remnants of alveolar walls that still exist. There is no recognizable epidermoid component. A. F. I. P. Acc. No. 218737–215.

Figure 184. Fat stain of tumor illustrated in figure 182, showing an abundance of fine fat-filled vacuoles in the tumor cells. Frozen section stained with Sudan IV. A. F. I. P. Acc. No. 218737–217.

Figure 185. Another histologic section of the tumor illustrated in figure 182. Bizarre multinucleated tumor giant cells are infiltrating the interalveolar septa. A. F. I. P. Acc. No. 218737–216.

Figure 186. Silver stain of tumor illustrated in figure 182 showing dense meshwork of argyrophilic fibers embracing individual cells and a few groups of cells. Laidlaw stain. A. F. I. P. Acc. No. 218737–218.

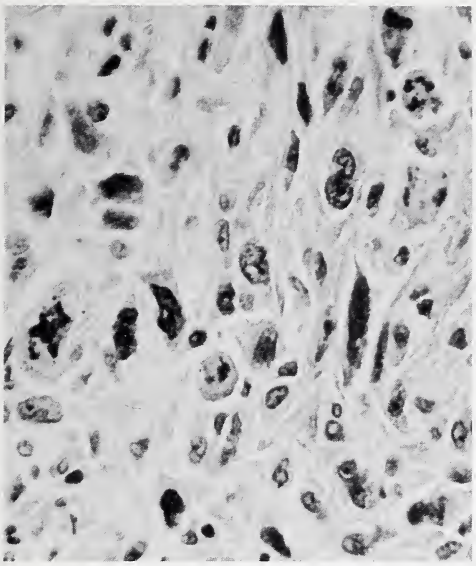

Fig. 183

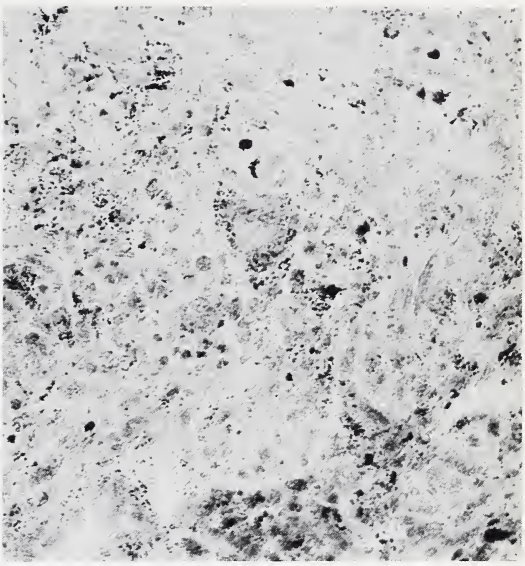

Fig. 184

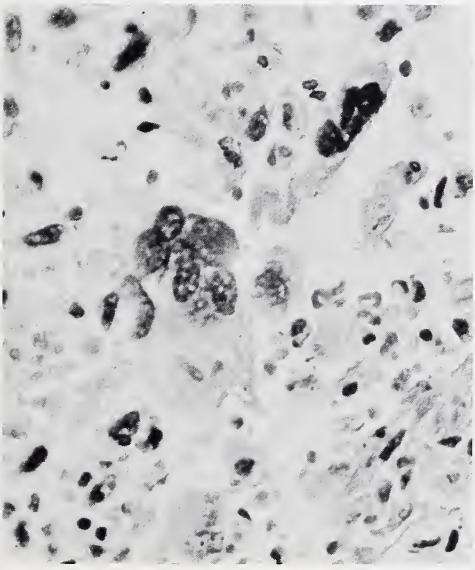

Fig. 185

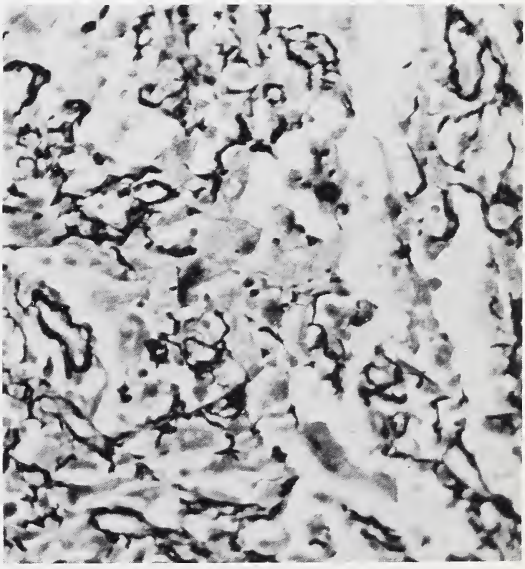

Fig. 186

is decreasing infiltration of the interalveolar septa, confirming the gross impression of a gradual merging with intact parenchyma.

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TUMORS OF DEVELOPMENTAL ORIGIN

HAMARTOMA

SYNONYMS AND RELATED TERMS: Adeno-chondroma; adeno-fibro-lipo-chondromyxoma; "bronchial hamartoma"; chondroma; hamartoblastoma; hamartochondroma; hamartoma chondromatosum pulmonis; lipo-chondro-adenoma; lipo-chondroma.

The name hamartoma is commonly employed for a group of complex tumors, usually of small size, situated in the periphery of the lung and consisting of proliferated elements of the bronchus in various proportions. They differ from the simple chondromas of the major bronchi in their more complex structure and more peripheral position. The term hamartoma was first applied by Albrecht in 1904. It comes from the Greek word meaning "to err," and is now generally applied to complex tumors where there is supposed to be, according to Albrecht's usage, an "abnormal mixing of normal components." It must be pointed out that in the lung these tumors do not differ essentially in structure from the fibroadenomas of the breast which Albrecht also considered to be hamartomas. These tumors cannot be classified as teratomas, since no tissues foreign to the lung are represented.

Two main types of hamartomas may be distinguished: the small circumscribed lesion of the adult; and the more massive, less circumscribed unencapsulated lesion, often lobar, of the newborn.

Hamartoma, Circumscribed Type

NATURAL HISTORY. The tumors are found once in approximately 400 individuals. They are two to three times more common in men. Since most hamartomas are minute and peripheral in position, they produce no symptoms and are found in routine films or at post mortem. There is roentgenographic evidence of their slow growth (figs. 187, 188). In the roentgenogram they ap-

pear as rounded shadows that may exhibit a striation with calcium that in the absence of cavitation or other evidence of tuberculosis should suggest hamartoma. Rarely one of these complex tumors may grow into and obstruct the lumen of a major bronchus. The larger tumors may compress bronchi in the same fashion as any space-occupying lesion appropriately placed within the thorax.

The question of the potential malignancy of these tumors is pertinent. In an instance reported by Simon and Ballon, there is suggestive histologic evidence of this, since in a most unusual partially unencapsulated tumor which involved a large part of the left lung of a 49-year-old man, it seemed to invade the parenchyma and the mediastinal fat, but there was no evidence of metastasis nor even of extension into the regional lymph nodes. This tumor contained primitive osteoid tissue as well as more mature bone and cartilage and some ductlike structures lined by ciliated epithelium.

GROSS. The circumscribed lesion in the adult is often subpleural, or at least peripheral in position, although a few tumors of similar structure have been described in the center of a lobe (fig. 191), or in the larger bronchi, where simple chondromas are relatively common. The size of these lesions varies from a few mm. up to 15 cm. Most of them are less than 1 cm. in diameter and are usually found incidentally at necropsy, when they are often mistaken for Ghon tubercles. When in the pleura these tumors may even be pedunculated. The external surface is usually nodular (fig. 189), and upon incision the lobular architecture responsible for this becomes apparent. The general background (figs. 190, 191) is blue-white and is usually interrupted by chalky white or yellow zones of calcification, and there may be streaks of bright yellow adipose tissue. Softening or minute cystic spaces may occasionally occur. These tumors are remarkably free of anthracotic pigment. They impinge on normal pulmonary substance or the pleura, and there is usually no surrounding consolidative process. With the larger lesions, bronchiectasis may result merely from displacement and compression of bronchi, as in the case of any intrapulmonary mass.

MICROSCOPIC. As in the fibroadenoma of the breast, there are thick communicating masses of stroma which carry before them into a divided lumen sheets of columnar or cuboidal epithelium, resembling that of the bronchi, but usually devoid of cilia (fig. 192). The stroma consists predominantly of masses of cartilage (hyaline, fibrous, or elastic) that merge peripherally with fibrous connective tissue. Within the latter, which acts as a support for the epithelium, are often embedded groups of fat cells or bundles of smooth muscle (fig. 193). Calcification or ossification may be in evidence in the cartilage or in the connective tissue. A few tumors contain no cartilage (fig. 194), but others consist largely of this material. Peripherally, there is a thin capsule of connective tissue which in some instances gives the impression that it is the residue of a thinned-out wall of a bronchiole, confirmed in some instances by close association with a sizable branch of the pulmonary artery (fig. 192).

TREATMENT. Since it is necessary to establish an accurate diagnosis when any intrathoracic tumor presents itself, exploration is indicated in view of the small risk of thoracotomy and the danger of allowing a malignant intrathoracic tumor to remain untreated. Tumors of this type have been resected without complication (figs. 189, 190). Since hamartomas are benign and there is ordinarily no associated bronchiectasis, utmost conservation of pulmonary tissue is indicated.

Hamartoma, Diffuse Type

The second type of hamartomatous lesion represents a major intrauterine malformation involving a large part or all of a lung. Here the supporting stroma may contain structures suggestive of bronchioles without proper relation to an alveolated parenchyma (although tissue resembling fetal lung may be present), and also may contain islands of cartilage, fat, and irregularly arranged blood vessels. When only a part of a lung is involved, these lesions may be circumscribed but not encapsulated (figs. 195, 196).

TERATOMAS

A few complex tumors have been described which show evidence of differentiation into tissues representative of all germ layers. Careful study is necessary to ascertain that the lesion has not metastasized from an extrapulmonary source, such as the testis. Especially difficult of interpretation is the teratoid neoplasm that involves not only the lung but also the mediastinum, where such tumors are not rare. In that instance, it is reasonable to presume that the mediastinum is the primary site.

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CIRCUMSCRIBED HAMARTOMA

(Figures 187 to 188 are from the same case)

Figure 187. Roentgenogram of the thorax showing a circumscribed hamartoma near the left hilum. There is no evidence of the calcification sometimes observed in these tumors. A. F. I. P. Acc. No. 218737–88.

Figure 188. Roentgenogram of the thorax four years later than that in figure 187. There is definite evidence of growth of the tumor. A. F. I. P. Acc. No. 218737–89.

Figure 189. Surgical specimen of the tumor shown in the roentgenograms in figures 187 and 188. The surface bosselations are typical of a circumscribed hamartoma. A. F. I. P. Acc. No. 218737–90.

Figure 190. Hemisections of two surgically resected hamartomas. Both were situated deep to the pleura of the right upper lobe. The glistening cut surfaces were of cartilaginous firmness except for the zone of softening indicated by the arrow. A. F. I. P. Acc. No. 218737–91.

Figure 191. Hamartoma discovered incidentally at necropsy. The irregular contraction of the cut surface is produced by zones of myxomatous connective tissue and fibrocartilage. The tumor is not associated with any grossly discernible bronchus. A. F. I. P. Acc. No. 218737–92.

Fig. 187

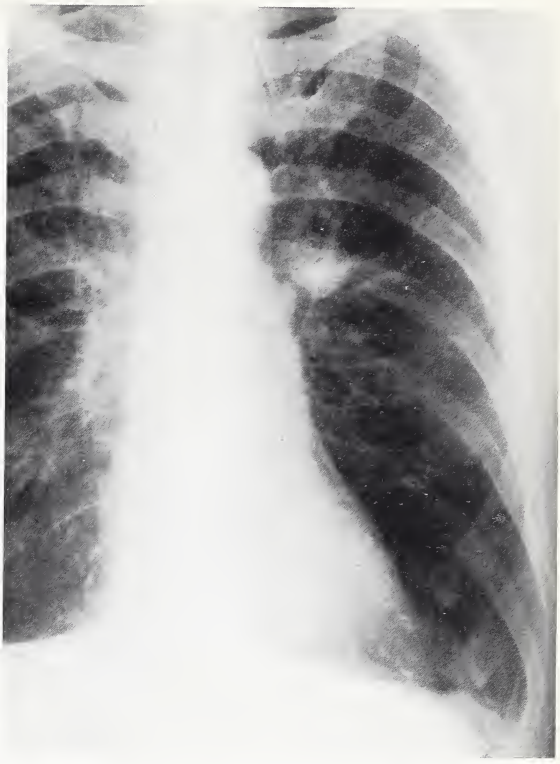

Fig. 188

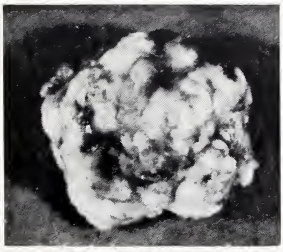

Fig. 189

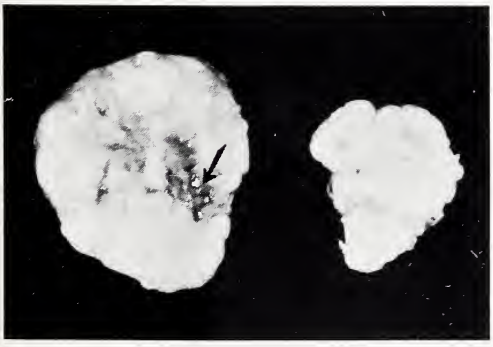

Fig. 190

Fig. 191

CIRCUMSCRIBED HAMARTOMA

Figure 192. Hamartoma found incidentally at necropsy. The structure is reminiscent of that of an intracanalicular fibroadenoma of the breast. Inclusions of cuboidal epithelium are found deep among the club-shaped masses of fibrocartilage. A large vessel abuts upon the lower margin of the tumor. This and the general arrangement of the tumor suggest the possibility of its origin in a bronchiole. × 27. A. F. I. P. Acc. No. 218737–67.

Figure 193. Hamartoma showing complexity of histologic structure. Epithelial spaces lined by mucus-producing epithelium and by ciliated low cuboidal epithelium ramify among supporting structures containing hyaline cartilage, fibrocartilage, adipose and fibrous connective tissue. × 35. A. F. I. P. Acc. No. 218737–93.

Figure 194. Tumor interpreted as an atypical hamartoma from the mediastinal aspect of the right lower lobe. Although possibly of mediastinal origin the tumor was embedded within the lung parenchyma. Cysts lined by ciliated columnar epithelium are found in a stroma containing large cells with abundant vacuolated cytoplasm. A. F. I. P. Acc. No. 218737–94.

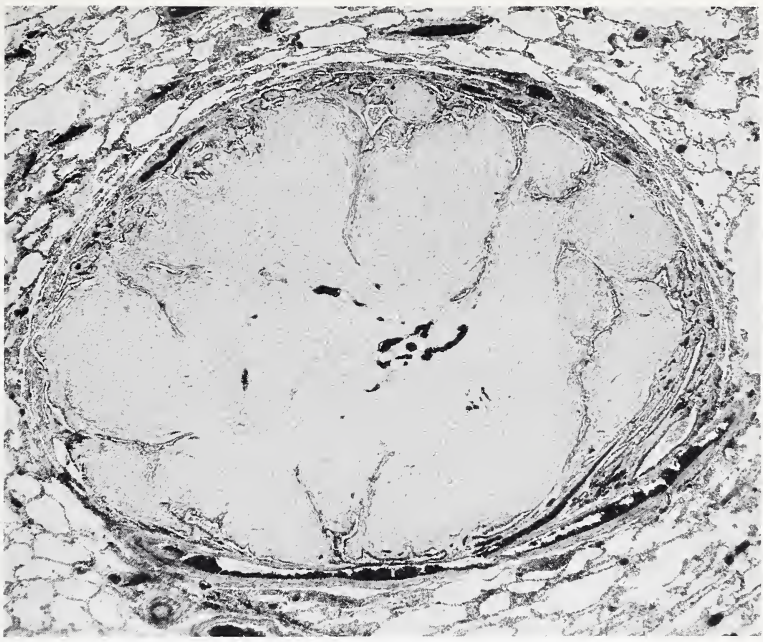

Fig. 192

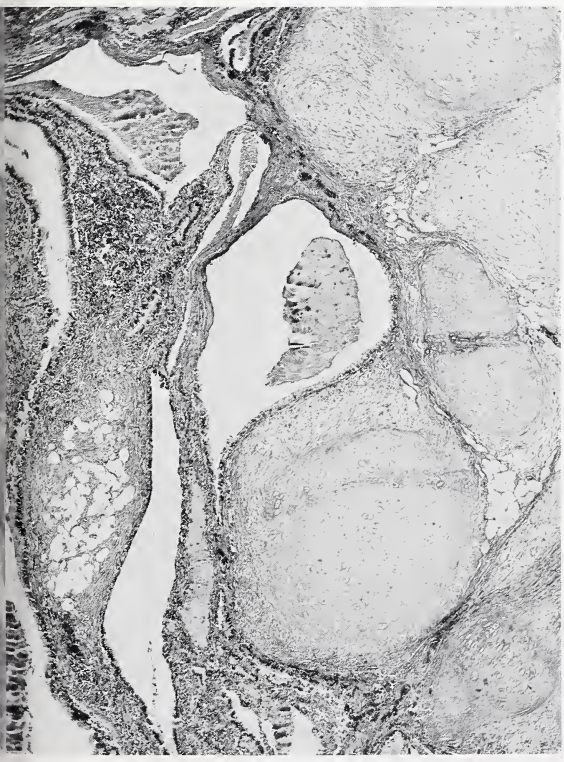

Fig. 193

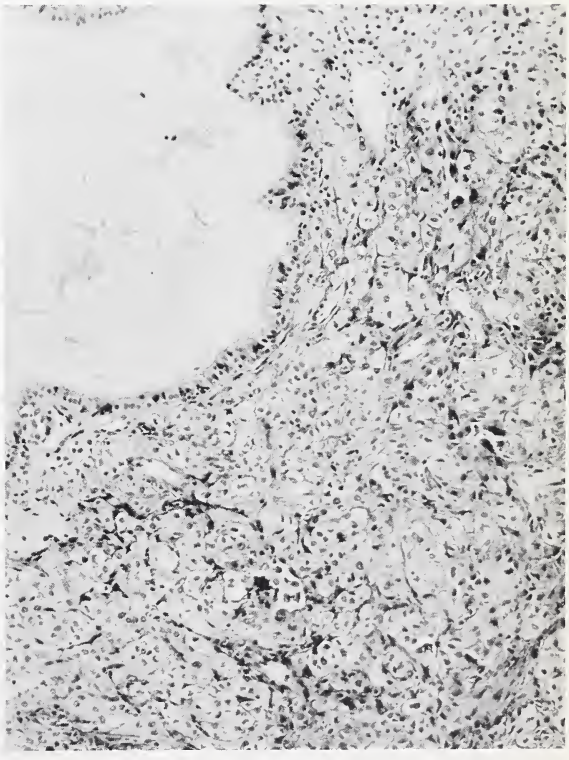

Fig. 194

DIFFUSE HAMARTOMA

(Figures 195 and 196 are from the same case)

Figure 195.* Hamartoma occupying almost the entire upper lobe of the right lung. A small portion of the middle lobe of the lung is also shown. A. F. I. P. Acc. No. 218737–95.

Figure 196.* A representative section of the hamartoma illustrated in figure 195. There are trabeculae of fibrous tissue containing dilated capillaries, islands of cartilage, and bronchiolar structures interspersed through the fetal lung tissue. × 24. A. F. I. P. Acc. No. 218737–96.

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*Jones, C. J. Unusual hamartoma of the lung in a newborn infant. Arch. Path., 48: 150–154, 1949. Figs. 1 and 2 are our figs. 195 and 196.

Fig. 195

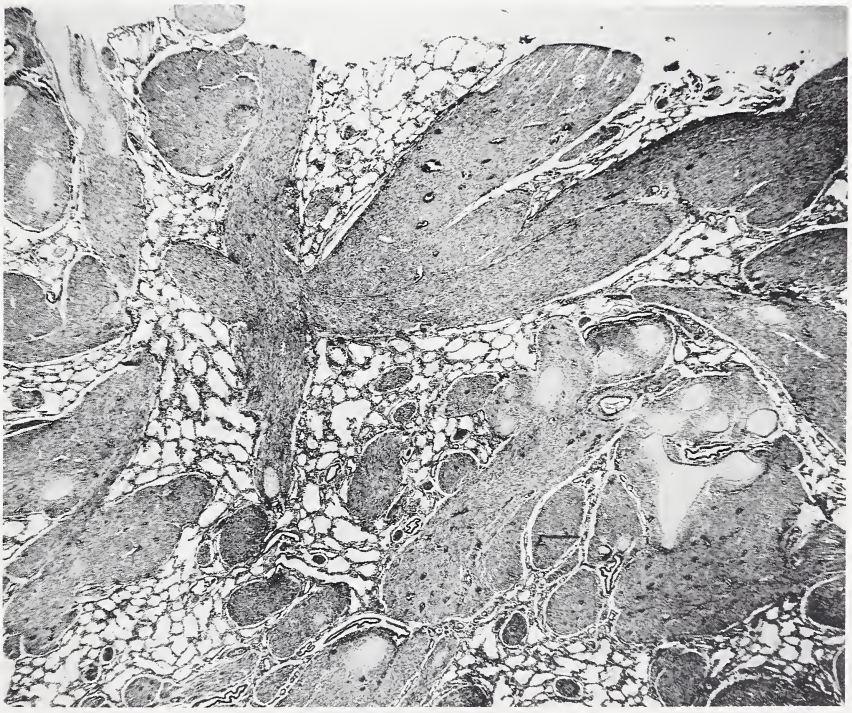

Fig. 196

DIFFERENTIAL DIAGNOSIS OF LUNG TUMORS

The growing awareness of physicians in general of the importance of the early diagnosis of bronchogenic carcinoma and the discovery of asymptomatic lung lesions in mass X-ray or fluoroscopic surveys make the differential diagnosis of lung tumors an increasingly common problem. It is complicated by the multiplicity of pathologic entities which may mimic, be mimicked by, or be coexistent with the various pulmonary neoplasms.

Occasionally all procedures fail, even thoracotomy, which is the last resort for undiagnosed lung lesions where bronchogenic carcinoma is suspected. It may be necessary to perform a lobectomy, and to keep the thorax open, while awaiting the results of an immediate thorough inspection, with frozen sections, of the resected lobe.

CLINICAL HISTORY. A careful history will disclose whether or not there have been: an exposure to tuberculosis or syphilis; a sojourn in the arid southwest of the United States where coccidioidomycosis is endemic; an occupational hazard in which there are dusts and fumes capable of producing the pneumoconioses, especially silicosis and asbestosis, beryllium granulomatosis or aspergillosis; personal habits whereby mineral oil has been ingested or used as nose drops leading to the possibility of paraffinoma of the lung.

BACTERIOLOGIC PROCEDURES. Examinations of the sputum and bronchial secretions should include in addition to cytologic studies, smears, cultures, and animal inoculations: for bacteria with especial emphasis on Mycobacterium tuberculosis; for higher bacteria with emphasis on Actinomyces israeli or Nocardia asteroides; for higher vegetable parasites with the emphasis on Coccidioides immitis, Aspergillus fumigatus, Cryptococcus hominis, Histoplasma capsulatum. Skin tests may be useful in tuberculosis, coccidioidomycosis, and histoplasmosis.

BIOPSY AND BRONCHOSCOPIC EXAMINATION. Biopsy of lymph nodes when enlarged may give clues to the possible presence of sarcoidosis, metastatic carcinoma, and lymphomas including Hodgkin's disease. Bronchoscopic examination and biopsy are the essential diagnostic procedures in any patient with the signs of bronchial obstruction, and may reveal in addition to the tumors in the major bronchi specific and nonspecific bronchitis, lymphadenopathy of any cause, endogenous and exogenous foreign bodies including foreign bodies originally lodging in the esophagus or penetrating the chest wall, and aberrant thyroid.

Aspiration biopsy may be profitable in an occasional peripheral lesion. In the differential diagnosis of such shadows the granulomas caused by the organisms mentioned in the section on Bacteriologic Procedures, gummas, bronchogenic cysts (see Fascicle 18, "Tumors of the Mediastinum"), echinococcus cysts, and lung abscesses should be considered.

BLOOD EXAMINATIONS. Examination of the cellular elements may be of some value aside from the well known changes due to pyogenic infection.

TABLE II.* INDETERMINATE LESIONS: FINAL DIAGNOSIS AS DETERMINED AT THORACOTOMY (111 Cases)

Diagnosis	Mass Lesions	Lesions Producing Bronchial Obstruction	Miscellaneous
Neoplastic			
Malignant			
Bronchiogenic carcinoma	35	23	2
Lymphosarcoma	...	1	...
Fibrosarcoma	1	...	...
Metastatic			
Osteogenic sarcoma	1	...	...
Adenocarcinoma	2	...	...
Benign			
Bronchial adenoma	2	1	3
Hamartoma	2	...	...
Teratoma	1	...	...
Endobronchial lipoma	...	1	...
Diffuse adenomatosis	...	1	...
Tumor-forming amyloid**	...	2	...
Inflammatory			
Chronic pneumonitis			
Suppurative with abscess	2	8	3
Lipoid	1	1	1
Secondary to broncholithiasis	...	2	...
Secondary to silicotic structure	...	...	1
Miscellaneous	...	5	...
Tuberculosis	3	1	...
Mycoses			
Actinomycosis	...	1	...
Coccidioidomycosis	2	...	...
Developmental			
Bronchial cyst	1	1	...
TOTAL	53	48	10

* Reprinted from Johnson, C. R., Clagett, O. T., and Good, C. A. The importance of exploratory thoracotomy in the diagnosis of certain pulmonary lesions. Surgery, 25: 218–230, 1949.

** Not a neoplasm—included here for reason of convenience.

Polycythemia should suggest arteriovenous fistula. An eosinophilia may be present in Loeffler's syndrome, the somewhat questionable chronic granulomatous form of which may be confused with bronchogenic carcinoma. Occasionally a mild eosinophilia may be seen in sarcoidosis. In monocytic leukemia the blood film is usually diagnostic.

Serologic tests are useful in the diagnosis of syphilis and coccidioidomycosis, and infestation with echinococcus.

X-RAY EXAMINATIONS. Mass films must be read promptly and patients with suspicious lesions should immediately have large chest films and whatever other tests necessary for diagnosis made if the mortality from bronchogenic carcinoma is to be reduced.

Sectional radiography in any of its technical variations and X-ray films of the chest taken at different angles are useful in localizing tumors.

Bronchography is occasionally of aid in visualizing intrabronchial neoplasms out of reach of the bronchoscope. Angiocardiography by outlining the blood supply may aid in differentiating an infiltrating from a circumscribed tumor. Caution should be exercised in interpreting angiocardiograms, since necrotizing, or cavitative lesions such as lung abscesses, may also produce localized failure of filling of the pulmonary vessels.

THORACOSCOPY. Diagnostic pneumothorax, supplemented by thoracoscopy, may be of aid in some instances.

THORACOTOMY. The wide variety of lesions which resist diagnosis short of thoracotomy and from which bronchogenic carcinoma cannot with certainty be distinguished are well illustrated in table II, taken from the report by Johnson, Clagett, and Good on 384 patients operated on by Dr. Clagett. Diagnosis was made in 270 patients without thoracotomy. Thoracotomy was done on 114 patients. In 111 of these a diagnosis was made as indicated in the table. The correct diagnosis was still unknown in the remaining three patients after the thoracotomy.

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METASTATIC CARCINOMA

(Figures 197–199 are from the same case*)

Figure 197. Emboli of neoplastic cells in pulmonary arteries from a carcinoma of the stomach. Some masses of tumor cells are well preserved. Others have become necrotic and, with the thrombi that have formed, are in process of organization. A. F. I. P. Acc. No. 218737–268.

Figure 198. Detail of figure 197. A. F. I. P. Acc. No. 218737–269.

Figure 199. Early and advanced organization of tumor emboli and thrombi within pulmonary arteries. A. F. I. P. Acc. No. 218737–270.

*Contributed by Dr. Roy Barnett, Norwalk, Conn.

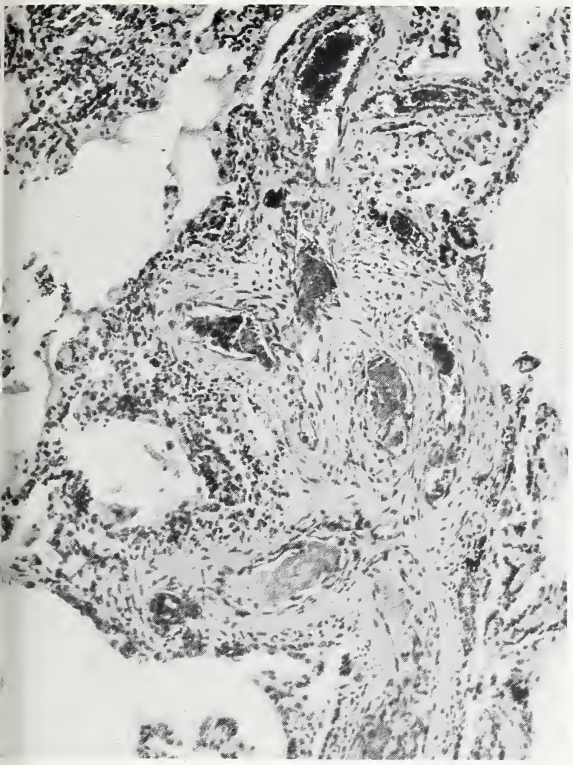

Fig. 197

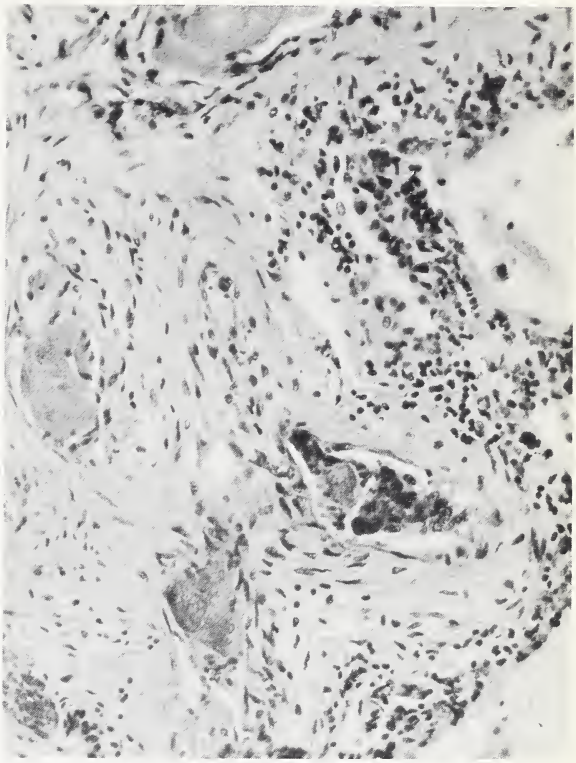

Fig. 198

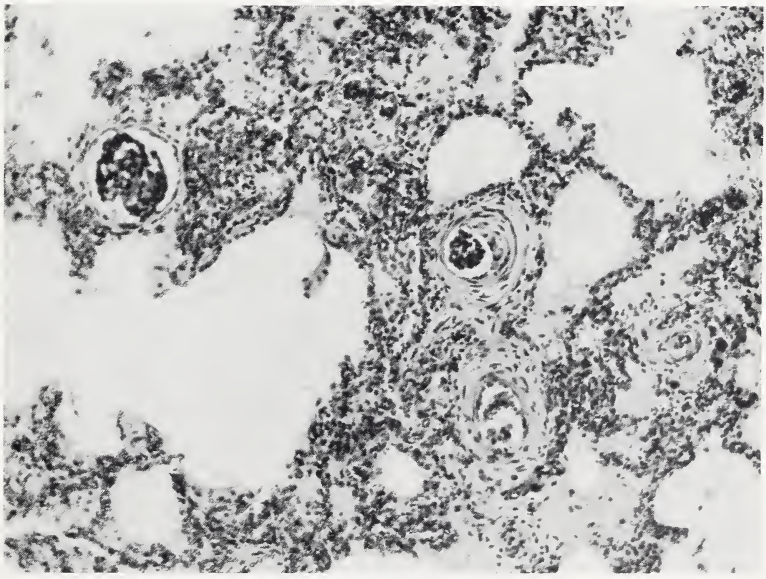

Fig. 199

METASTATIC TUMOR IN LUNG

Figure 200. Chorionepithelioma of testis metastatic in lung. There are three isolated, sharply demarcated nodules resembling clotted blood. A. F. I. P. Acc. No. 218737–227.

Figure 201. Pulmonary metastasis of a carcinoma primary in the breast. The main lower lobe bronchus is thickened by mucosa lymphatic infiltration in a manner suggesting that of primary carcinoma of the lung (figs. 74, 75, 77). Blood vessels at the hilum have been compressed and there is an infarct of the lower lobe. A. F. I. P. Acc. No. 218737–230.

Figure 202. Multiple isolated metastases in lung from carcinoma primary in the liver. A bronchus has been invaded and obstructed by the tumor. A bronchial lymph node also contains metastatic tumor tissue. A. F. I. P. Acc. No. 218737–229.

Fig. 200

Fig. 201

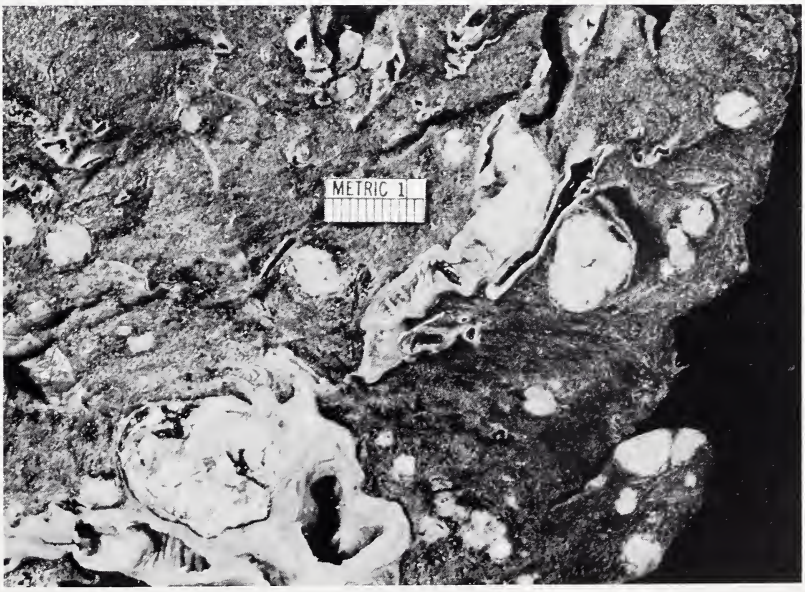

Fig. 202

NEOPLASTIC LESIONS OF THE LUNG OTHER THAN PRIMARY TUMORS

METASTATIC TUMORS

Multiple tumors within the lung should be considered metastatic until proved otherwise. Hematogenous metastases to the lungs are frequent, as would be expected from the position of the lung as a filter. The pathway to the lungs may be by systemic venous channels including the vertebral veins (Batson). Metastases may be in the form of myriads of minute emboli that may be invisible in the roentgenogram, but so extensive as to produce a functionally important degree of obstruction to the outflow of the right ventricle, with cor pulmonale (figs. 197–199).

Metastases to the contralateral lung may be by way of the bronchial arteries, or veins, or by lymphatic channels. Hematogenous metastases are often discrete and spherical, as in those derived from renal and testicular tumors, sarcomas, and chorionepitheliomas (figs. 200–202). Necrosis may, however, modify the shape of metastases, and they may conform to the curvature of the pleura (fig. 204).

The lungs also have rich lymphatic connections with the structures about the crura of the diaphragm, such as the liver and adrenals, and the celiac and lumbar groups of lymph nodes. Metastasis to the lung from carcinoma of the breast is frequently by way of the intercostal lymphatics, particularly along the substernal vein to the parietal pleura with shedding of cells in the pleural cavity and subsequent implantation of carcinoma on the visceral pleura.

Many tumor emboli seeding the capillary bed of the lungs are either nonviable or are destroyed before they can invade and multiply to form a metastasis. Once the tumor has gained access to the lung, by whatever route, and set up a metastasis, it is redistributed from this way station in the manner of a primary tumor. Many metastatic lesions spread radially along the lymphatics that accompany the bronchovascular rays (figs. 204, 209, 210). This gives the typical "explosive" roentgenographic pattern (fig. 209).

Aspirative spread is illustrated in figure 206 and is a possible mechanism of spread of tumors on the surface of the oropharynx and trachea to the lungs. Coelomic spread through the pleural cavity is frequently observed in both primary and secondary lung tumors.

Isolated or multiple metastases to the lung occur even many years after removal of the primary lesion (figs. 203, 205–208), and their resection is worth while in association with treatment of the primary tumor.

An isolated metastasis may center about (fig. 201) and even invade (figs. 203, 205, 206) a bronchus so as to suggest a primary lesion. Polypoid, intra-

METASTATIC TUMOR IN LUNG

Fig. 203

Fig. 204

Figure 203. Right lobectomy specimen. This isolated metastasis from a carcinoma of the large intestine protrudes finger-like into the bronchus. The primary tumor had been resected one year before. A. F. I. P. Acc. No. 218737–228.

Figure 204. Lymphogenous metastases to lung and pleura from epidermoid carcinoma, primary in cervix. A nodule in the upper lobe abutting upon the pleura takes the contour of the interlobar fissure. A. F. I. P. Acc. No. 218737–8.

METASTATIC TUMOR IN LUNG

(Figures 205–208 are from the same case)

Figure 205. Pulmonary metastases from a carcinoma of the kidney. An elongated extension from a large metastasis in the apex of the lower lobe projects into the apical bronchus of the right lung. The primary tumor had been resected 16 years before the patient's death. A. F. I. P. Acc. No. 218737–233.

Figure 206. Basal segment of the lower lobe of the right lung shown in figure 205. Both metastases are largely intrabronchial and polypoid, with a relatively small base of attachment. The location and appearance suggest possible aspiration into the basal bronchi of tumor from the larger metastasis illustrated in figure 205. A. F. I. P. Acc. No. 218737–234.

Figure 207. Histologic section of a polypoid intrabronchial metastasis from the lung illustrated in figures 205 and 206. The tumor tissue is remarkably similar to that of the primary renal tumor. There is no necrosis and mitoses are rare. A. F. I. P. Acc. No. 218737–235.

Figure 208. Histologic section from the lung illustrated grossly in figures 205 and 206 showing metastatic carcinoma within a lymphatic. A. F. I. P. Acc. No. 218737–236.

Fig. 205

Fig. 206

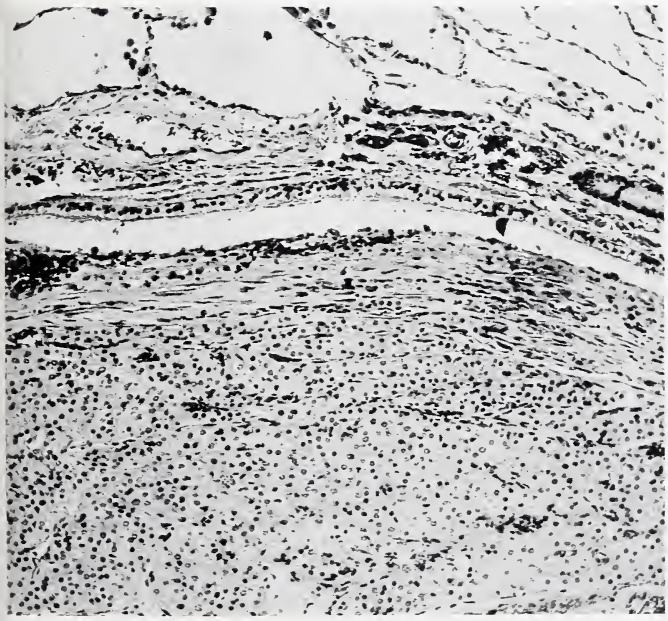

Fig. 207

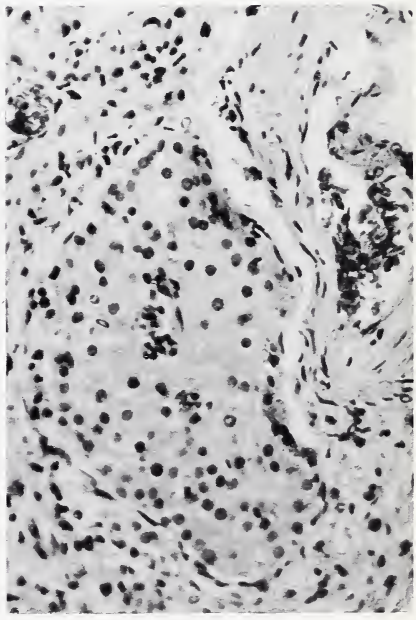

Fig. 208

bronchial, obstructing metastases are most common with metastases from the colon (especially the rectum) and kidney, but occur also in instances of carcinoma of the breast and other sites. It is possible to obtain a positive bronchoscopic biopsy in 16 percent of such lesions (Seiler, Clagett, and McDonald). Bulky growth of metastatic tumor tissue within the lymphatics of the bronchial mucosa (fig. 201) or external compression by lymph nodes may also restrict the lumen, with consequent distal atelectasis or pneumonitis. Infarction of the lung resulting from compression of vessels (fig. 201) is more frequent in metastatic than in primary tumors of the lung.

Symptoms when present differ in order of frequency from those found in primary lung neoplasms. Farrell in a study of 78 cases, proved at autopsy, found the following symptoms attributable to metastatic pulmonary lesions: dyspnea (23 cases); cough (15 cases); pain (9 cases); expectoration (6 cases); hemoptysis (2 cases); hoarseness (1 case).

A few cases are reported in the literature of unexplained regression or disappearance of presumed pulmonary metastases following removal of the primary tumor, with or without supplemental therapy. The inherent difficulty in all these reports is the lack of histologic evidence of metastasis.

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LYMPHOMAS AND LEUKEMIAS

Lymphoblastomatous and leukemic lesions of all types may involve the lymphatic tissue of the mediastinum and lung and extend to a degree into the parenchyma. (For primary lymphosarcoma of the lung see section on Malignant Parenchymal Tumors.) In three conditions especially, Hodgkin's disease,

METASTATIC TUMOR IN LUNG

(Figures 209 and 210 are from the same case)

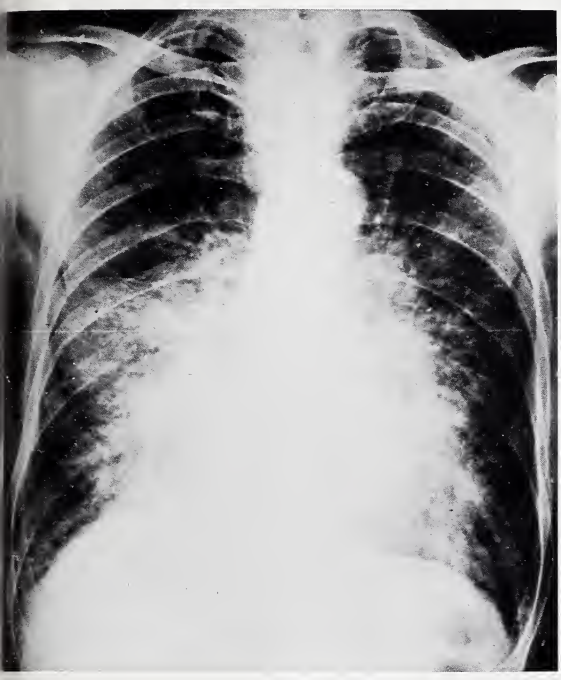

Fig. 209

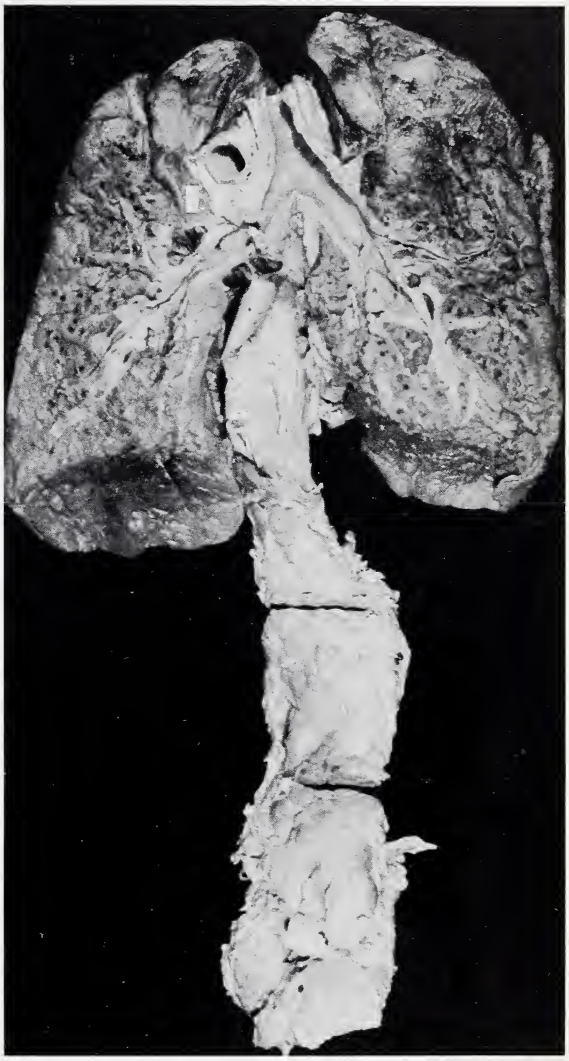

Fig. 210

Figure 209. Roentgenogram of chest showing shadows typical of lymphogenous metastases. Primary is in the prostate. (Compare with figure 210.) A. F. I. P. Acc. No. 218737–231.

Figure 210. Carcinoma of prostate with lymphatic permeation of aortic and mediastinal tissue, bronchovascular rays, and pleura of lung. The cut surface of the prostate is seen at the bottom of the photograph. Thick collars of translucent gray-pink tissue are visible about the bronchi and vessels. A. F. I. P. Acc. No. 218737–232.

HODGKIN'S DISEASE OF LUNG

(Figures 211 and 212 are from the same case*)

Figure 211. A large cavity has been produced by necrosis in the center of a mass involving the lung of a patient with Hodgkin's disease. × 20. A. F. I. P. Acc. No. 204613–1.

Figure 212. Detail of figure 211. Numerous Reed-Sternberg cells can be seen in a mixed exudate which also contains lymphocytes, plasma cells, large mononuclear cells, eosinophiles and polymorphonuclear leucocytes. The neutrophiles predominate within the necrotic material close to the lumen. × 250. A. F. I. P. Acc. No. 204613–2.

*From the files of the Armed Forces Institute of Pathology.

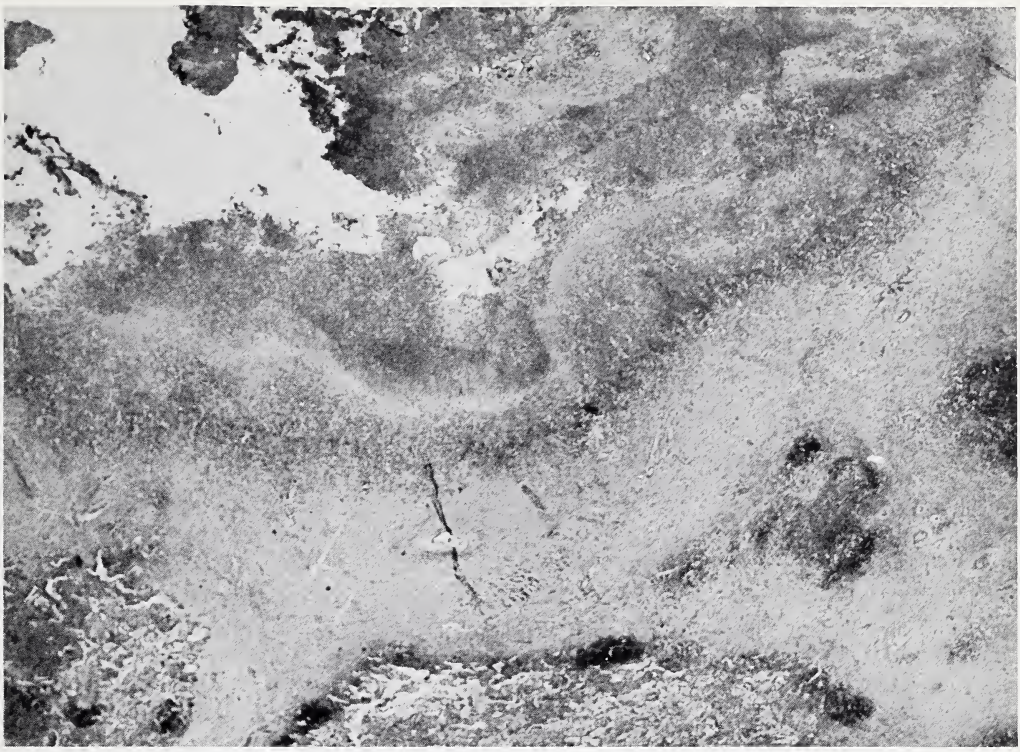

Fig. 211

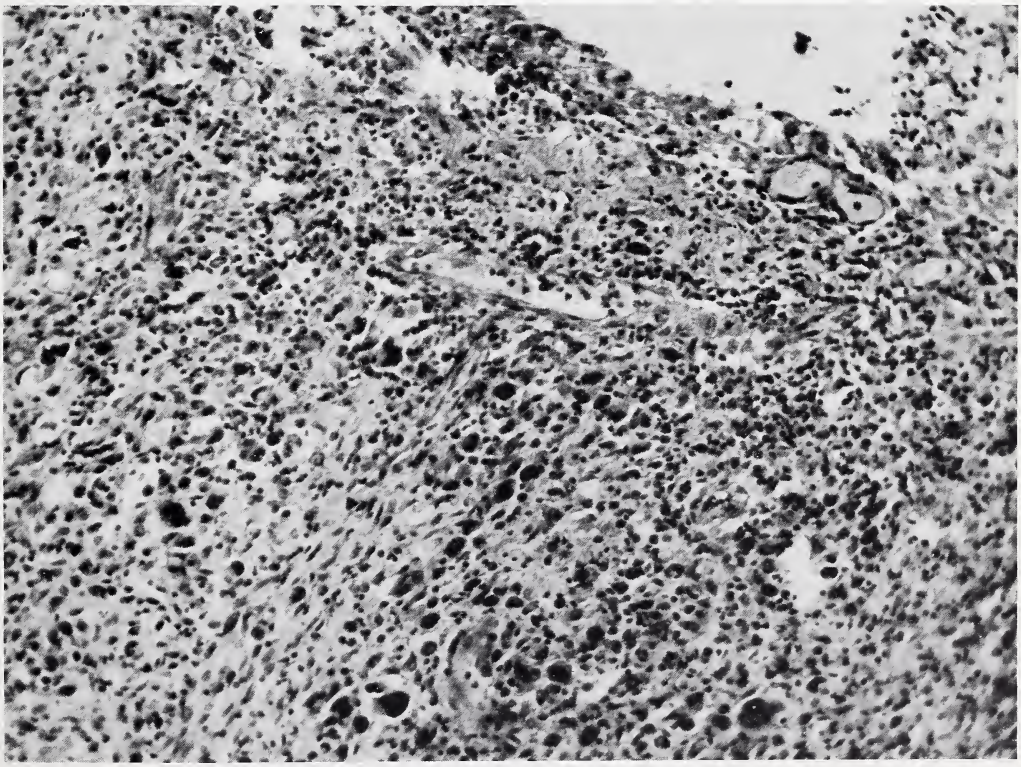

Fig. 212

NONLIPID RETICULOENDOTHELIOSIS (LETTERER-SIWE'S DISEASE)

(Figures 213–219 are from the same case)

Figures 213.* Bronchogram of right side showing no evidence of bronchiectasis despite the remarkably fine reticular cystic and fibrosing process that involves both lungs. Diaphragm is flattened. The patient was a 32-year-old man who first developed a readily controlled diabetes insipidus two and one-half years before his death. Subsequently he developed external otitis and skin lesions. No bony defects were demonstrated by X-ray. The most distressing symptoms were dyspnea, cough without sputum, and migratory chest pain beginning about a year before his death and increasing progressively to the terminal pulmonary insufficiency. A. F. I. P. Acc. No. 218737–219.

Figure 214.* The sectioned right lung at autopsy. Similar changes were found in the left lung. Note the spongy architecture due to the transformation of the lung, especially the lower half, into a series of large and small thick-walled cavities with glistening lining membranes. There is now some bronchiectasis involving small bronchi, but the cavities do not represent wide expansions of the bronchi. Typical lesions of nonlipid reticuloendotheliosis were found in the hilar lymph nodes but not in the spleen. A. F. I. P. Acc. No. 218737–19.

Figure 215.* Detail of figure 214. A. F. I. P. Acc. No. 218737–6.

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*From Dennis, J. W., and Rosahn, P. D. The primary reticulo-endothelial granulomas, with report of an atypical case of Letterer-Siwe's disease. Am. J. Path., 27: 627–653, 1951. Figures 2, 3, and 4 are our figures 213, 214, and 215.

Fig. 213

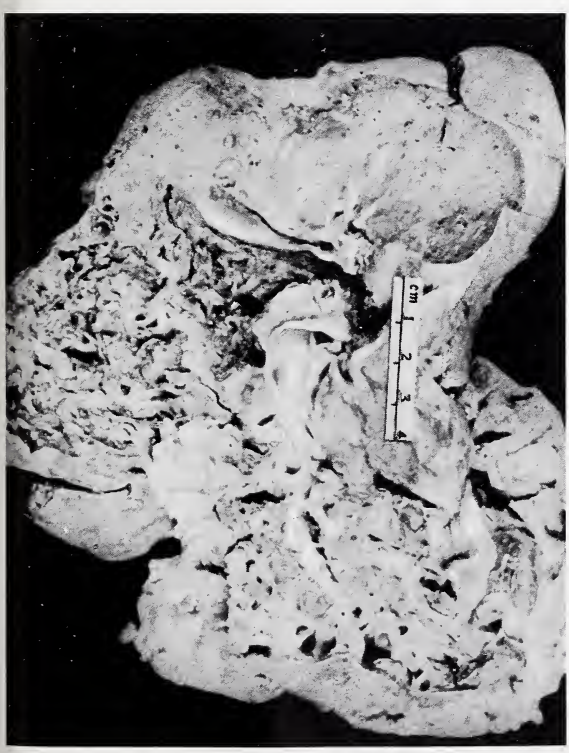

Fig. 214

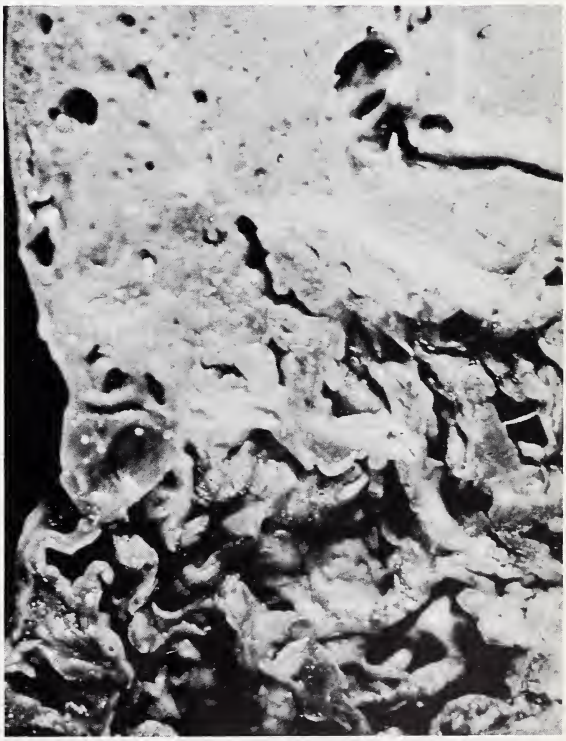

Fig. 215

NONLIPID RETICULOENDOTHELIOSIS (LETTERER-SIWE'S DISEASE)

(Figures 213–219 are from the same case)

Figure 216. Histologic section from the less involved tissue shown grossly in figure 215. Some of the interalveolar septa have become thickened, others have disappeared thus forming cavities which are lined by tissue such as is pictured in figure 218. × 7. A. F. I. P. Acc. No. 218737–220.

Figure 217. Histologic section of the more extensively cavitated portions of lung shown in figure 215. Many interalveolar septa have been lost leaving a thick investment of atypical tissue about bronchovascular rays. There is no obvious necrosis. × 7. A. F. I. P. Acc. No. 218737–221.

Figure 218.* Histologic section from an area in the lung in which the cells are poorly differentiated with relatively little cytoplasm and prominent nucleoli. One cell is in mitosis. A. F. I. P. Acc. No. 218737–223.

Figure 219.* An unusual instance of involvement of the mucous membrane of a bronchiole. The atypical tissue consists of polymorphous elements in the reticulum cell large mononuclear series accompanied by eosinophiles. Some of the former resemble mature macrophages; others are undifferentiated forms. A. F. I. P. Acc. No. 218737–222.

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*From Dennis, J. W., and Rosahn, P. D. The primary reticulo-endothelial granulomas, with report of an atypical case of Letterer-Siwe's disease. Am. J. Path., 27: 627–653, 1951. Figures 5 and 7 are our figures 218 and 219.

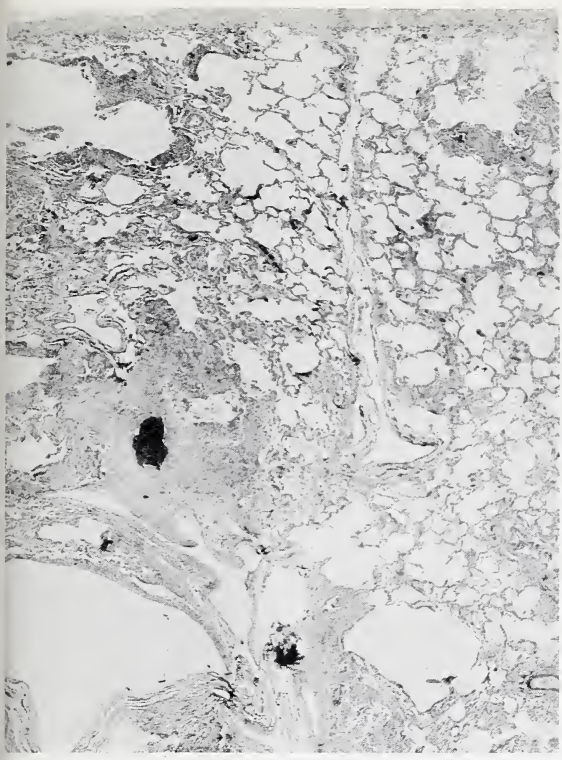

Fig. 216

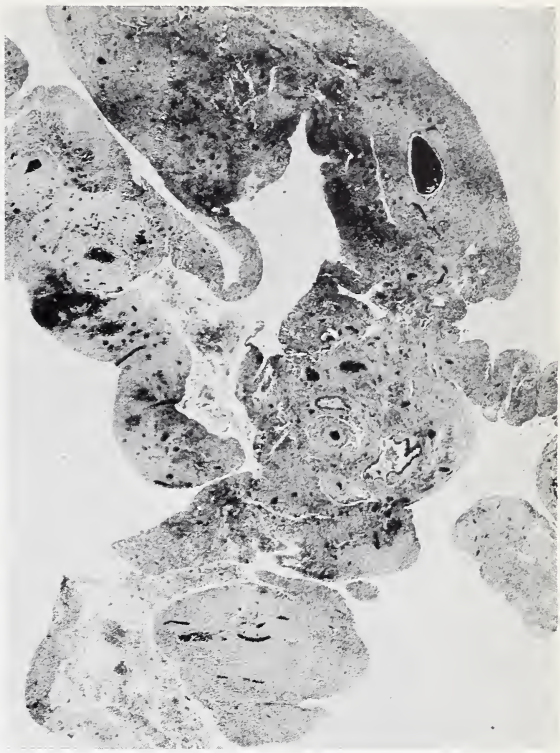

Fig. 217

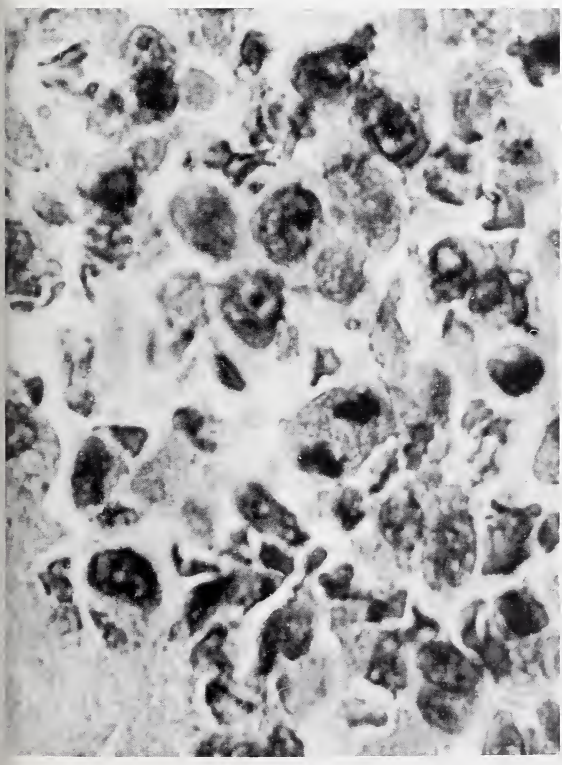

Fig. 218

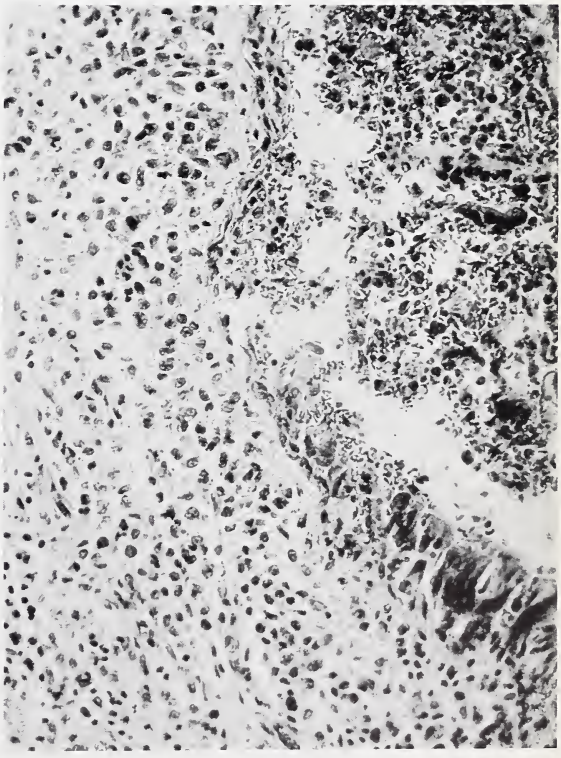

Fig. 219

MONOCYTIC LEUKEMIA

(Figures 220–223 are from the same case)

Figure 220. Roentgenogram taken of the chest when the patient was admitted. A. F. I. P. Acc. No. 218737–224.

Figure 221. Roentgenogram of the chest taken shortly before the patient died. There are fine radially distributed opacities throughout both lung fields. A. F. I. P. Acc. No. 218737-225.

Figure 222. Cut surface of lung at necropsy. There is a remarkably homogeneous consolidation (see figure 223). A. F. I. P. Acc. No. 218737–72.

Figure 223. Histologic section of the gross specimen shown in figure 222. An interalveolar septum abutting upon a bronchovascular ray is thickened by numerous immature and mature large mononuclear cells, some in mitosis. A. F. I. P. Acc. No. 218737–226.

Fig. 220

Fig. 221

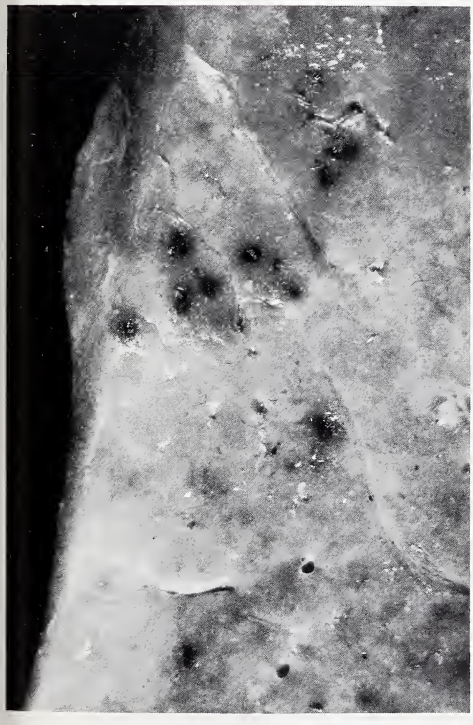

Fig. 222

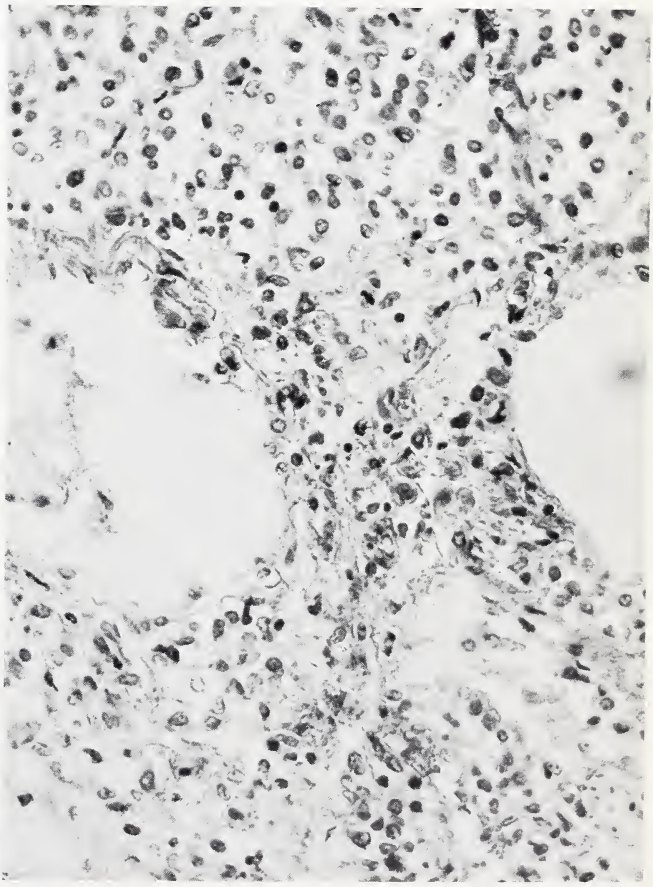

Fig. 223

nonlipid reticuloendotheliosis (Letterer-Siwe's disease), and monocytic leukemia, the patient may complain of symptoms that draw attention to the lung as the chief seat of disease even when the process is generalized. In varieties of leukemia other than monocytic, immature elements may be found within the alveoli, especially about masses of bacteria and foci of necrosis.

Hodgkin's Disease

It is common to find the lung infiltrated in varying degrees in Hodgkin's disease, especially in the lymphoid tissue. In rare instances the patient may present a chronic cavitative process in the lung, and he may have febrile episodes, cough, and sputum. Even the mediastinal nodes may appear to be enlarged only to a degree compatible with a chronic necrotizing and organizing pneumonia. A lesion from such a patient is illustrated in figures 211 and 212.

Nonlipid Reticuloendotheliosis (Letterer-Siwe's Disease)

The lung is often involved in nonlipid reticuloendotheliosis. Here proliferation of the reticuloendothelial cells may be active in the walls of the alveoli and also within their lumina. In children "emphysema" has been described, but in reality this is a subtle cavitation of the lung that has not been considered in the necessary detail, especially since the disease is not confined to children, and the evidences of pulmonary involvement may dominate the clinical course. A case of this disease (figs. 213–219) that came to necropsy at the New Britain General Hospital illustrates the main features and is presented with the permission of Dr. P. D. Rosahn.

Monocytic Leukemia

In monocytic leukemia (as well as in reticuloendotheliosis), the lungs may be the seat of a proliferative process so extensive as to present a gradual fine radial "clouding" of the lung fields in the roentgenogram (figs. 220, 221). Upon this may be superimposed finely nodular opacities representing both foci of proliferation, and of the necrotizing and hemorrhagic pneumonitis that may occur in any leukemia. Ultimately the lungs may be completely consolidated with a translucent pale pink cut surface, interrupted only by occasional foci of hemorrhage and necrosis (fig. 222). The proliferation is most extensive about the bronchovascular rays, but is in progress also in the interalveolar septa, especially where these abut upon the rays (fig. 223).

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TUMORS OF THE PLEURA

Considerable uncertainty exists as to the exact origin of the diffuse or localized tumors adjacent to or filling the pleural space. Pleural origin is presumed for localized tumors from the position of the tumor; in most tumors it is impossible to be certain of the fact. Few accept Robertson's extreme view that diffuse primary neoplasms of the pleura do not exist, although rigid criteria for the diagnosis have only rarely been fulfilled. The absence of a primary lesion outside of the pleura must be established by a most thorough gross and microscopic scrutiny of the viscera, especially of the lungs. Metastatic lesions may give the gross appearance and even a suggestive histologic appearance of a primary lesion in a serous membrane. "Mesothelial lining cells" may appear to merge by a series of transitional forms with neoplastic cells of a metastasis.

It is convenient to subdivide tumors presumed to be primary in the pleura into localized or diffuse forms, despite uncertainties as to histogenesis. The localized tumors usually have the structure of cellular fibromas or fibrosarcomas, or sometimes of differentiated connective or neural tissues. The diffuse tumors are probably derived from mesothelium.

Localized Tumors of the Pleura

NATURAL HISTORY. Localized tumors of the pleura are usually encountered in routine chest films or as an incidental finding at necropsy. Symptoms, when they exist, are of pain in the chest, dyspnea, and at times cyanosis and clubbing of the fingers. There is roentgenographic evidence that some of these tumors are very slow in growth and less malignant clinically than would be suggested by their histologic structure. The tumors may reach a gigantic size without metastasis, since they are usually not highly invasive (figs. 228, 229). It may be possible to resect these localized forms without recurrence.

GROSS. The tumor may involve either the visceral or parietal layer of the pleura, and it is impossible to say from the gross whether the lesions are truly of pleural origin (fig. 224). Some may be derived from the lung itself or subpleural tissue of the body wall, with reflection of the pleura by the neoplasm in the manner of a capsule. Some of these tumors are pedunculated and there may be bandlike adhesions across the pleural space. Some tumors may reach a huge size while remaining well encapsulated. In other instances, especially in the malignant variants, the tumor is invasive. The pleural cavity often contains fluid that may reach a very large volume requiring frequent thoracenteses. Metastases are rare except to the local lymph nodes.

TUMORS OF THE PLEURA

(Figures 224 and 225 are from the same case. Figures 226 and 227 are from the same case*)

Figure 224. Histologic section of a well differentiated fibroma discovered incidentally at necropsy. It arose within or just beneath the pleura. × 8. A. F. I. P. Acc. No. 218737–60.

Figure 225. Detail of figure 224. A few elongated fibroblasts are seen in interlacing ribbons of collagen. × 160. A. F. I. P. Acc. No. 218737–40.

Figure 226. Histologic section fibrosarcoma (?) of pleura. The tumor was localized, lobulated, and measured 15 x 12 x 10 cm. × 75. A. F. I. P. Acc. No. 213156–1.

Figure 227. Detail of figure 226. Small ovoid and spindle-shaped cells, occasionally in mitosis, are seen in a collagenous stroma. Some tumors of this sort yield cells resembling mesothelium when explanted into tissue cultures. × 250. A. F. I. P. Acc. No. 213156–2.

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*Contributed to the Armed Forces Institute of Pathology by Dr. Nathan B. Friedman, Cedars of Lebanon Hospital, Los Angeles, Calif.

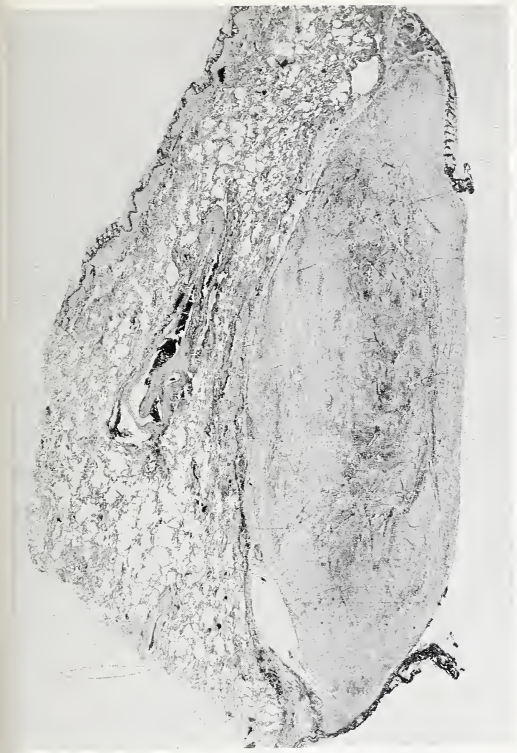

Fig. 224

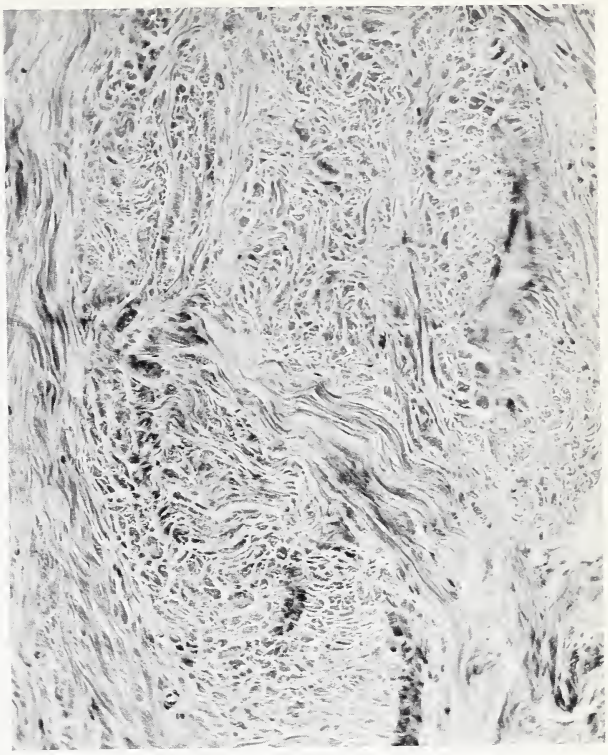

Fig. 225

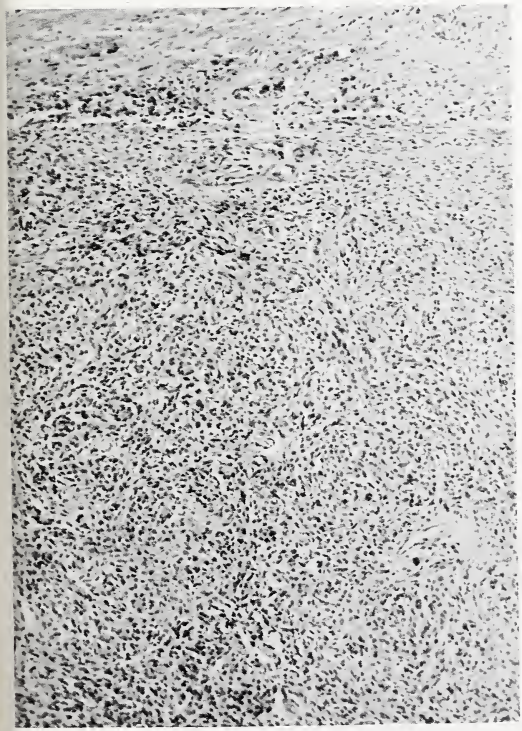

Fig. 226

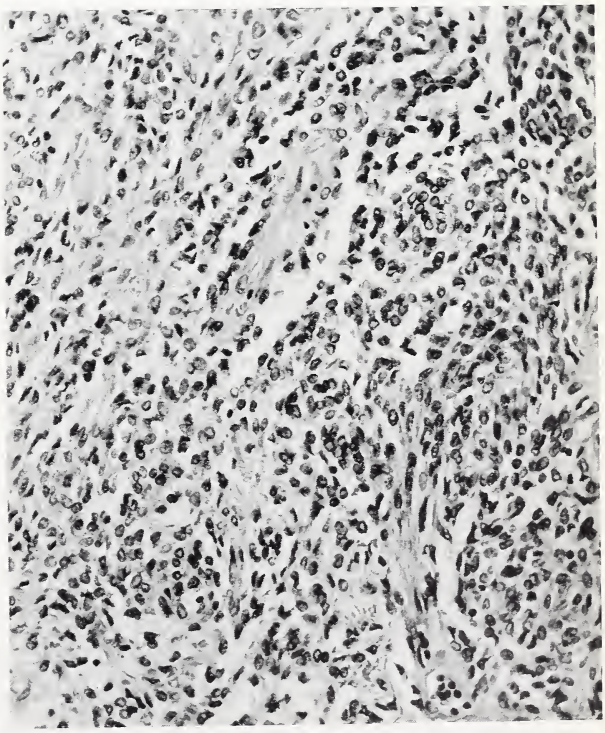

Fig. 227

LOCALIZED SARCOMA OF THE PLEURA

(Figures 228–231 are from the same case*)

Figure 228. Cut section of an enormous mass involving the visceral pleura of the posterior surface of the left lung. Foci of necrosis and areas of cystic degeneration can be seen. The specimen was obtained at autopsy from a 55-year-old man who for one and a half years before admission had suffered from ankle edema, weakness, and fatigue, and had had a weight loss of 55 pounds. One year prior to admission a "questionable area" of increased density was noted in the region of the left apex by X-ray. Two weeks prior to admission he complained of a sharp pain in the axillary region over the ninth rib. A thoracentesis yielding 300 cc. of fluid relieved the pain. Shortly thereafter, a roentgenogram showed a large homogeneous density filling almost the entire left hemithorax, compressing the lung anteriorly and inferiorly and displacing the heart and mediastinal content several centimeters to the right. There was no evidence of calcification. The interpretation was that both tumor and fluid were present in the left chest. A. F. I. P. Acc. No. 218737–274.

Figure 229. Posterior view of specimen shown in figure 228, demonstrating the encapsulation of the mass and the medial as well as anterior displacement of the left lung. A. F. I. P. Acc. No. 218737–275.

Figure 230. Histologic section of a hyalinized portion of the tumor. A. F. I. P. Acc. No. 218737–276.

Figure 231. Histologic section of a more cellular part of the pleural sarcoma showing masses of spindle-shaped cells, some in mitosis. A. F. I. P. Acc. No. 218737–277.

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*Case of Dr. Irving Akerson, Bridgeport, Conn.

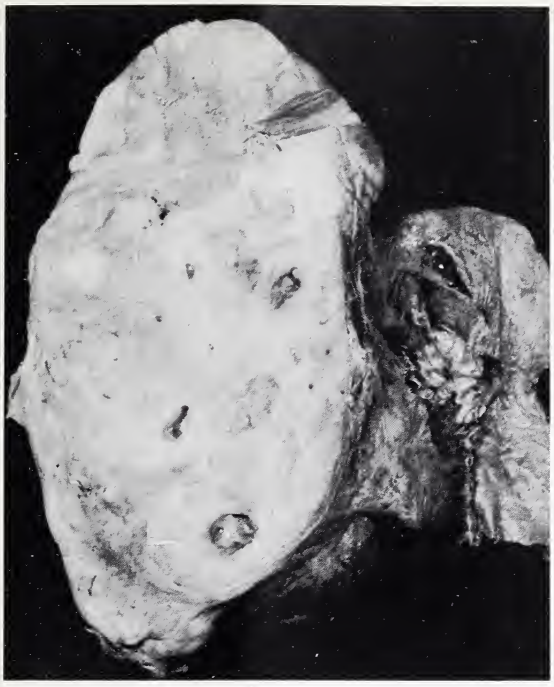

Fig. 228

Fig. 229

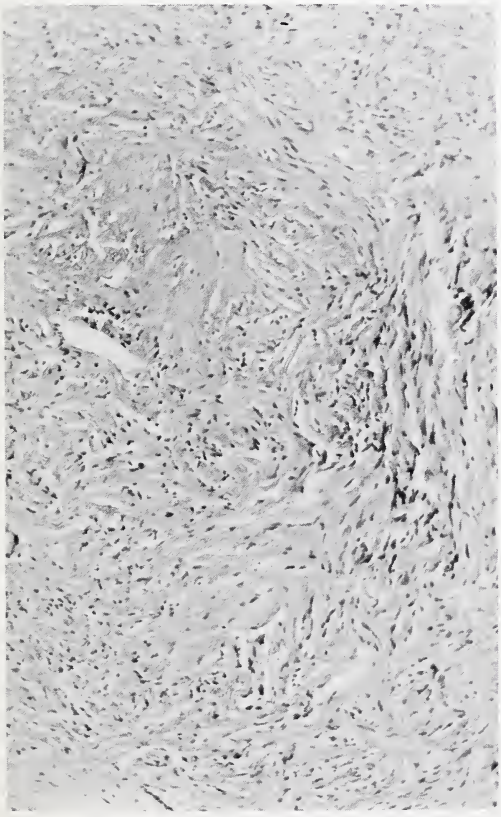

Fig. 230

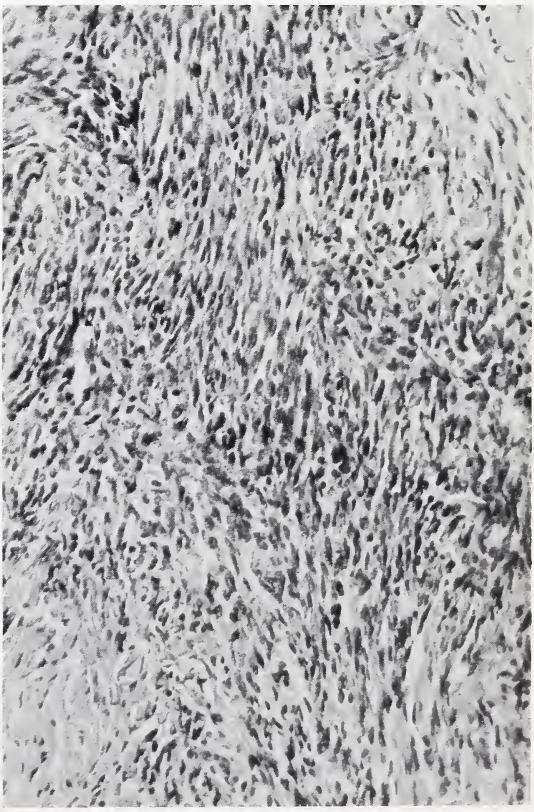

Fig. 231

MICROSCOPIC. Localized pleural tumors may have the histologic structure of fibroma (figs. 224, 225), neurofibroma, osteofibroma, lipoma, fibrosarcoma (figs. 226, 227, 230, 231), chondrosarcoma, etc. Some contain several mesenchymal tissues, and have been given the name "mesenchymoma." The cellular fibromas or fibrosarcomas are the most common. Some localized tumors consist of very well differentiated collagenous tissue. It is obvious that some of these tumors may well be of subpleural origin.

To be differentiated from true pleural tumors are organized pleural exudates in patients with a history of empyema. These tumor-like masses have been described by Brown and Johnson under the term "pseudo-tumors" of the pleura.

Mesothelioma

SYNONYMS AND RELATED TERMS: Adenoendothelioma; alveolar endothelial sarcoma; carcinoma; carcinosarcoma; endothelial carcinoma; endothelial sarcoma; endothelioma; endothelioma carcinomatodes; fibroendotheliosis of pleura; lymphangioendothelioma; lymphangitis carcinomatodes; lymphangitis proliferans; mesothelial carcinoma; perithelioma; pleural carcinoma; pseudo-sarcoma of pleura; sarcocarcinoma; sarcoendothelioma; sarcoma; serosal epithelioma.

True primary diffuse tumors of the pleura are far fewer than have been reported as such, since in most reports evidence is lacking that a sufficiently thorough search has been made for a primary source, especially in the lung. Only in the absence of such a primary can a diagnosis of mesothelioma of the pleura be made.

There are no sharply defined structural features that would with certainty distinguish a mesothelioma. Most acceptable as primary mesotheliomas are such examples as case 5 in Klemperer and Rabin's report where the tumor suggested a carcinomatous structure in some parts and sarcomatous in others, where connective tissue fibrils were demonstrated to embrace the individual cells in both parts, where the patient was youthful, and where no metastases were found to exist.

The mesothelium of the serous membrane, the subserous connective tissue, and lymphatic endothelium have all been considered as the tissue of origin for the diffuse tumor. It seems possible from the tissue culture studies of Stout and Murray that even certain tumors that consist of spindle-shaped cells may be of mesothelial origin. These tumors that resemble epithelium may reasonably be considered to be of mesothelial origin, since derivation of epithelial structures from coelomic mesoderm occurs in normal embryogenesis. There is no evidence that lymphatic endothelium is the source of many, if any, of these tumors.

Statements concerning these tumors, as regards metastasis for example, vary greatly, depending upon how rigidly the criteria for the diagnosis of mesothelioma are applied. A large correction factor must therefore be applied to statements that follow, in the realization that a certain proportion of metastatic tumors may have been included.

NATURAL HISTORY. The maximum incidence appears to be between 41 and 50 years of age, with considerable numbers in the immediately preceding and subsequent decades. Males are predominantly involved in the ratio of five to three. Symptoms are like those of the localized form, but the clinical course is often rapid with fatal termination.

GROSS. Despite the diffuse nature of the process, the cavity of the pleura is almost always preserved and it contains serous or serosanguineous fluid. Both the visceral and parietal layer including the diaphragmatic surface may be involved. The walls of this cavity may have a thickness as great as 15 cm.; there may be irregular plaques and nodules, with predominant thickening of one or the other layer. At times the thickened tissue produces an appearance suggesting that of a trabeculated bladder (pl. III–C). The interlobar fissures and pulmonary septa also become filled with tumor that projects shelfwise into the lung. This makes the search for a primary tumor in the lung all the more difficult.

MICROSCOPIC. The more usual microscopic appearance resembles carcinomatous tissue, at times in combination with a sarcomatous structure or on occasion a pure sarcomatous pattern. The former may be of the "simplex," epidermoid, or glandular type (figs. 233, 234, 236). The status of the epidermoid type is the most dubious, especially in view of the well founded suspicion that most of the apparently pleural tumors are metastatic; nevertheless, proliferated but not neoplastic mesothelium may resemble epidermoid carcinoma rather closely. In the form resembling adenocarcinoma, the acini may contain mucinous material. The structure may at times be papillary. Some tumors have an arrangement in sheets and whorls suggesting that of meningioma (figs. 237, 238).

METASTASES. Statements concerning metastases again are rendered inaccurate to the same degree as the true primary status of the pleural neoplasm is in doubt. According to Stout and Murray, these tumors are invasive but usually do not metastasize beyond the mediastinal nodes. Fischer, however, gives not only a rate of metastasis of 96.5 percent to the regional lymph nodes, but also states that the opposite lung is involved in 75 percent, the pericardium in over 33 percent, and that more widespread metastases may occur with involvement of the same organs as in carcinoma of the lung.

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MESOTHELIOMA OF THE PLEURA

(Figures 232–236 and plate III–C are from the same case)

Figure 232. Histologic section of parietal pleura from the specimen shown in plate III–C, demonstrating that the trabeculation is the result of irregularly proliferating fibrous connective tissue. The cells on the surface have the appearance of proliferated mesothelium, such as might be seen in organizing pleurisy. A. F. I. P. Acc. No. 218737–240.

Figure 233. Mass of irregular cells in loose stroma within the fibrous parietal pleura. One cell is in mitosis. Mitoses were only rarely found. A. F. I. P. Acc. No. 218737–242.

Figure 234. Histologic section of visceral pleura. Irregular tumor acini penetrate the elastica to enter the superficial portion of the lung parenchyma (lower part of photograph). This occurred in many places. Verhoeff elastic stain. A. F. I. P. Acc. No. 218737–244.

Figure 235. Groups of cells, arranged as in "carcinoma simplex," infiltrating the parietal pleura. A. F. I. P. Acc. No. 218737–241.

Figure 236. Cells in acinar arrangement within dense fibrous stroma invading extrapleural fat. A. F. I. P. Acc. No. 218737–243.

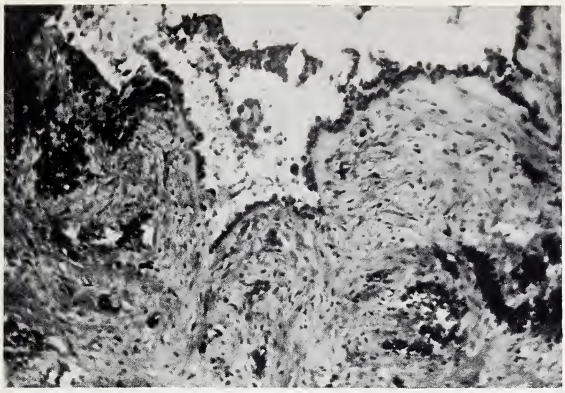

Fig. 232

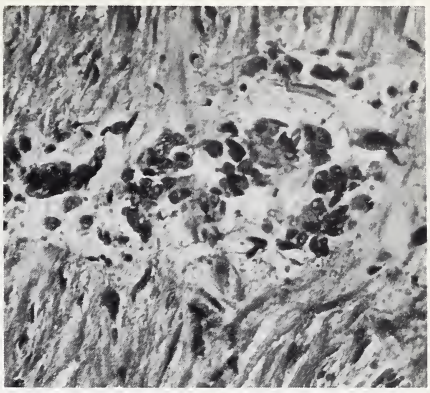

Fig. 233

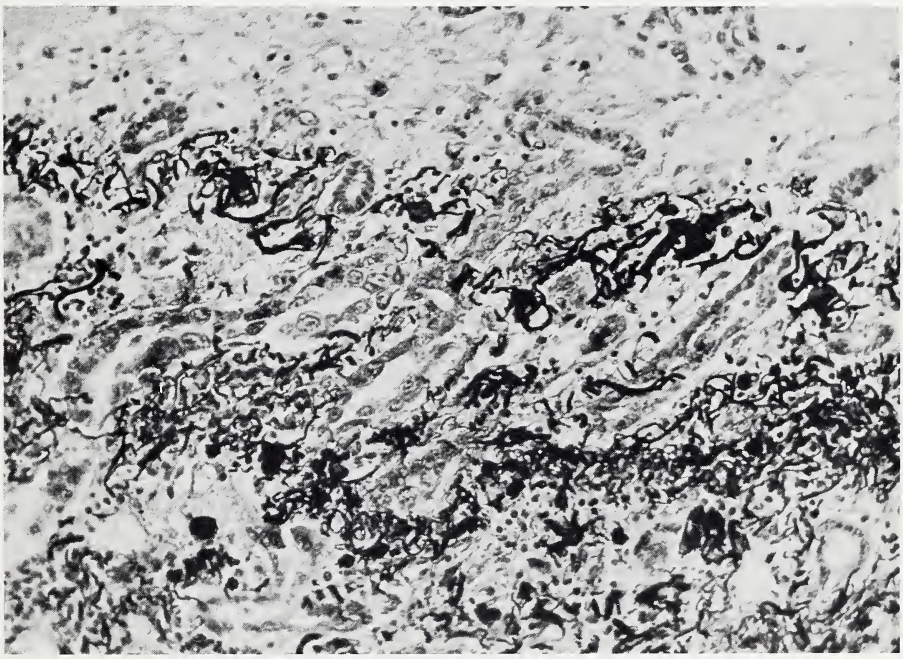

Fig. 234

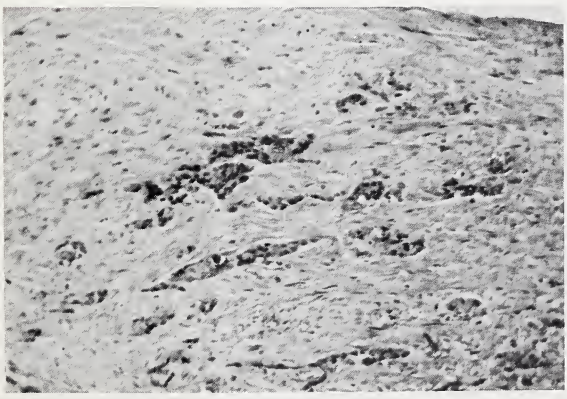

Fig. 235

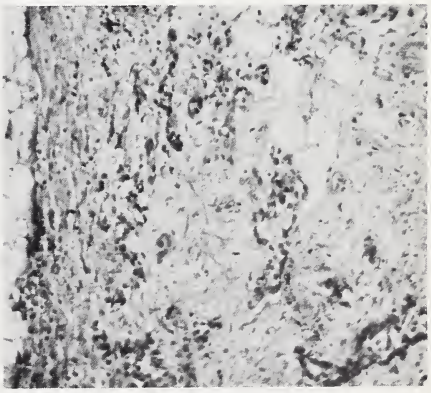

Fig. 236

TUMORS OF THE PLEURA

(Figures 237 and 238 are from the same case)

Figure 237. Histologic section of one of numerous nodules involving both the visceral and parietal pleura of a 27-year-old man. The large sheet of tumor is penetrated by a delicate vascular stroma. The patient died after an illness lasting two months. No extension of the tumor into the parenchyma of the lung and no metastases were found at necropsy. × 115. (From the Armed Forces Institute of Pathology.) A. F. I. P. Acc. No. 92946–1.

Figure 238. Detail of figure 237. The appearance is somewhat suggestive of meningioma, but the cells are compatible with proliferating mesothelium. Mitoses are rare, despite the rapid clinical course. Some of the cells are whorled but there are no intercellular bridges. × 390. (From the Armed Forces Institute of Pathology.) A. F. I. P. Acc. No. 92946–2.

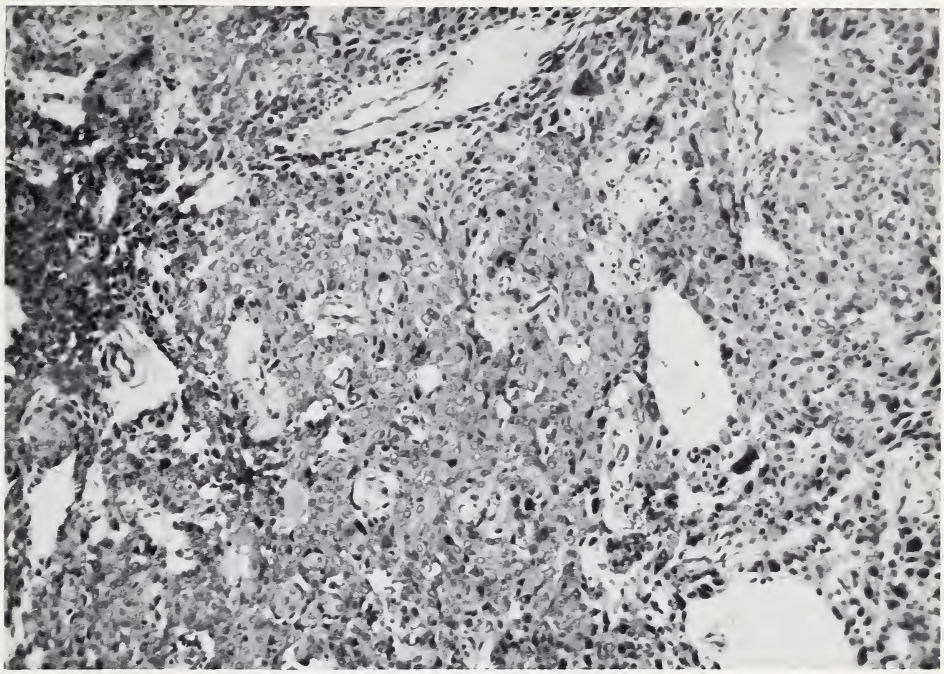

Fig. 237

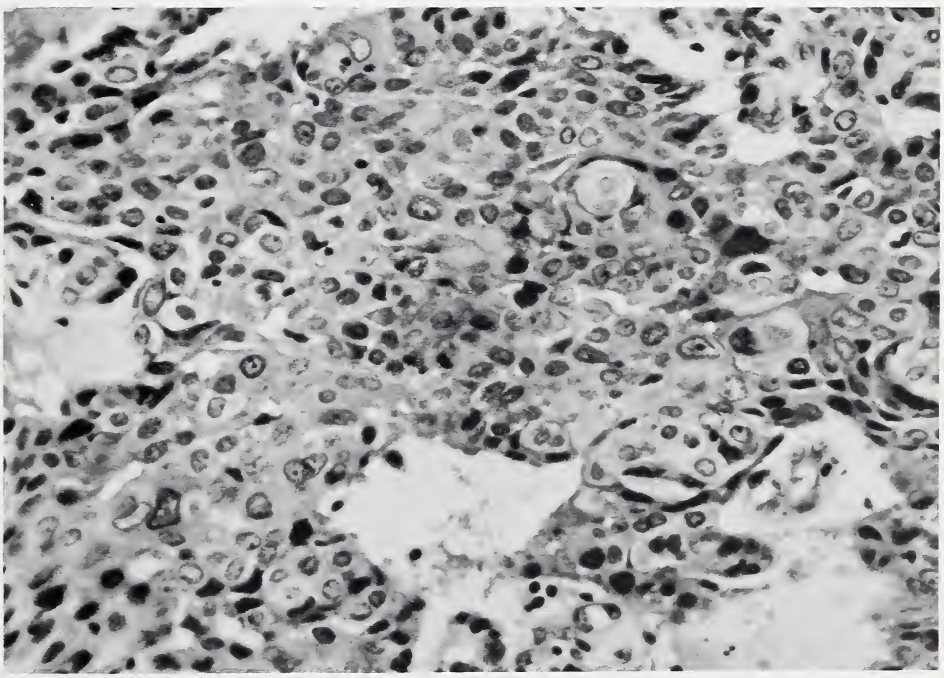

Fig. 238

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TUMORS OF THE DIAPHRAGM

It often becomes a matter of definition whether a particular tumor is classified as of diaphragmatic, pleural, or peritoneal origin. So few of these tumors have been described that only some general statements can be made. Both benign and malignant tumors have been described.

Among the benign tumors are fibromyoma (Bonamy, 1912, quoted by Binney), angiofibroma, lipoma, and others of mixed structure. A lipoma, described by Söderlund, produced severe pain relieved after surgical extirpation of the tumor. A fibroma found incidentally at necropsy is illustrated in figures 246 to 248. Lymphangiomatous tumors with an abundant adipose stroma attached to the diaphragm at or near the foramen of Morgagni may resemble pericardial cysts roentgenographically (figs. 239–242). These cysts may be uniocular or are composed of locules of variable size which intercommunicate, which possess a smooth lining, and which contain clear or somewhat opalescent serous fluid. Smooth muscle in the wall of the lymphatic cysts, abundant lymphoid tissue, and obvious small lymphatic channels with a structure identical with the walls of the larger locules distinguish the lymphangiomatous from the pericardial cysts on microscopic examination.

In figures 243 to 245, a tumor is illustrated that was attached to and received its blood supply from the left dome of the diaphragm. Histologically, it has the structure compatible with that of a bronchogenic cyst but does not contain cartilage.

Most malignant tumors that have been described have contained at least some elements suggesting an origin from muscle tissue—as the fibromyosarcoma reported by Sauerbruch (quoted by Binney), rhabdomyosarcomas, an undifferentiated myosarcoma, and a leiomyosarcoma. Most of these had metastases in the mediastinal lymph nodes, lungs, and liver. A malignant tumor composed of polymorphous elements suggesting those of a rhabdomyosarcoma, but lacking striations, is illustrated in figure 249.

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LYMPHANGIOMA OF DIAPHRAGM

(Figures 239–242 are from the same case)

Figure 239. Posterior-anterior roentgenogram of the thorax. A. F. I. P. Acc. No. 218737–245.

Figure 240. Lateral roentgenogram of the thorax showing the relationship of the radiopaque cyst to the costophrenic angle. A. F. I. P. Acc. No. 218737–246.

Figure 241. Resected surgical specimen. The vascular pedicle (clamped) was attached to the diaphragm in the region of the interval between the sternal and costal portions on the right. The greatest dimension of the cyst was 9.5 cm. The single locule of the cyst had a trabeculated lining and contained a clear fluid. A. F. I. P. Acc. No. 218737–247.

Figure 242. Histologic section of the wall of the cyst. Flat endothelial cells form the lining. Bundles of smooth muscle, lymphoid tissue, and numerous lymphatic channels are in the wall. A. F. I. P. Acc. No. 218737–248.

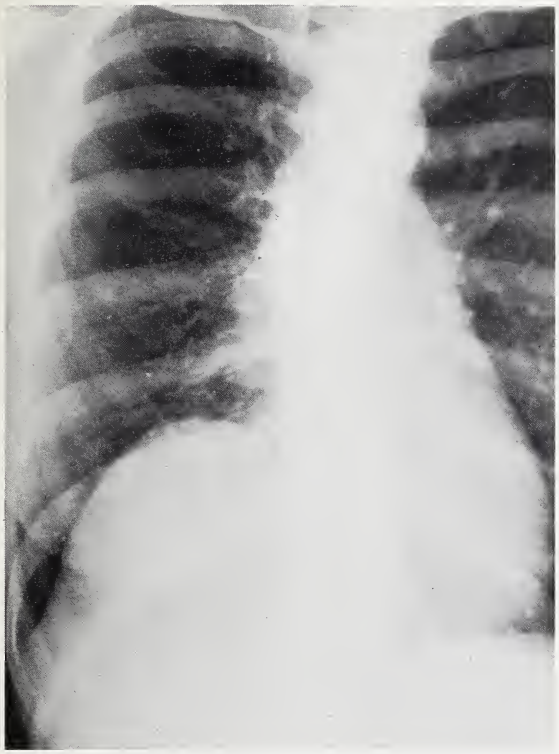

Fig. 239

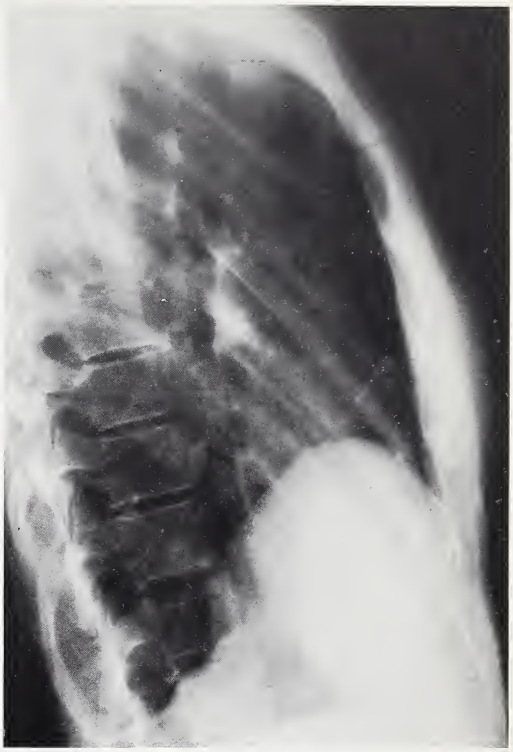

Fig. 240

Fig. 241

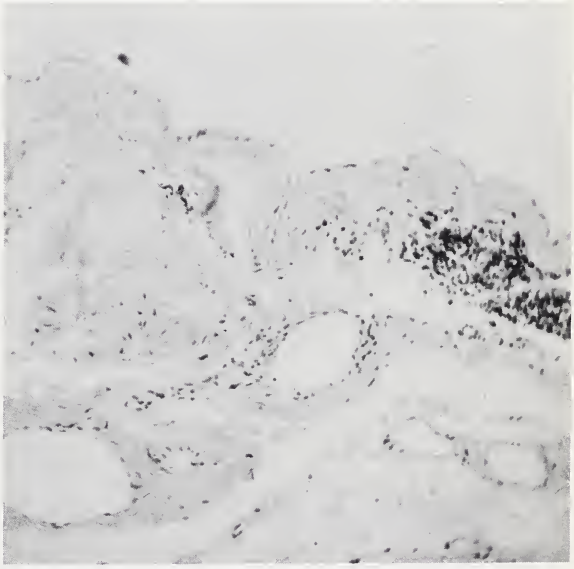

Fig. 242

CYST OF DIAPHRAGM

(Figures 243–245 are from the same case)

Figure 243. Multiloculated bronchogenic (?) cyst attached by a vascular pedicle (clamped) to the left leaf of the diaphragm approximately 5 cm. anterior to the esophageal hiatus. The broad channels ramifying upon the surface are of lymphatic origin. Filmy fibrous adhesions attached the cyst to the lower lobe of the left lung. A. F. I. P. Acc. No. 218737–253.

Figure 244. Cut surface of the bisected cyst shown in figure 243. The multiple locules are filled with clear, viscous, mucoid material. A. F. I. P. Acc. No. 218737–254.

Figure 245. Histologic section of the wall of the cyst illustrated in figures 243 and 244 showing the linings of several locules. The lining epithelium is ciliated low columnar or cuboidal epithelium on a fibrous stroma in which are large lymphatic and smaller blood-filled channels. A. F. I. P. Acc. No. 218737–255.

Fig. 243

Fig. 244

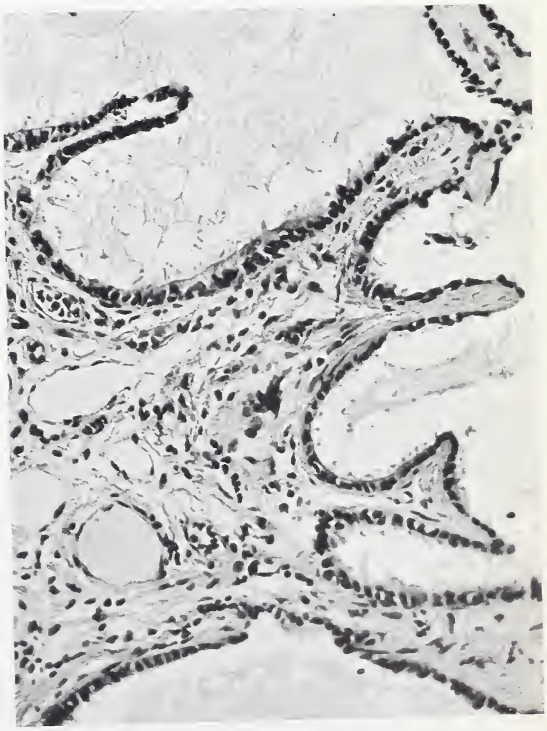

Fig. 245

TUMORS OF THE DIAPHRAGM

(Figures 246–248 are from the same case*)

Figure 246. Fibroma of the diaphragm. The encapsulated tumor is shown in situ from above. It had a narrow pedicle. Large vascular channels can be seen in the capsule. A. F. I. P. Acc. No. 218737–78.

Figure 247. Histologic section from the less cellular portion of the tumor shown in figure 246. Elongated narrow fibrous tissue cells are seen in a collagenous stroma. A. F. I. P. Acc. No. 218737–256.

Figure 248. Histologic section from another more cellular area of the tumor shown in figure 246. A. F. I. P. Acc. No. 218737–257.

Figure 249. Histologic section of a tumor interpreted as a rhabdomyosarcoma. There are numerous large polymorphous cells, often multinucleated and frequently in mitosis. No striations were seen but the general structure is highly suggestive of rhabdomyosarcoma. The patient was a 35-year-old man who had symptoms of cough and pain in the chest beginning two months before death. At autopsy the left leaf of the diaphragm was thickened and continuous with a tumor mass in the center. There was extension to the pleura on the left and metastases to the liver, mediastinal and abdominal lymph nodes, gastrointestinal tract, spleen, kidneys, heart, and bone marrow. × 545. (From the Armed Forces Institute of Pathology.) A. F. I. P. Acc. No. 109354–4.

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*Case of Dr. Rolf Katzenstein, Meriden, Conn.

Fig. 246

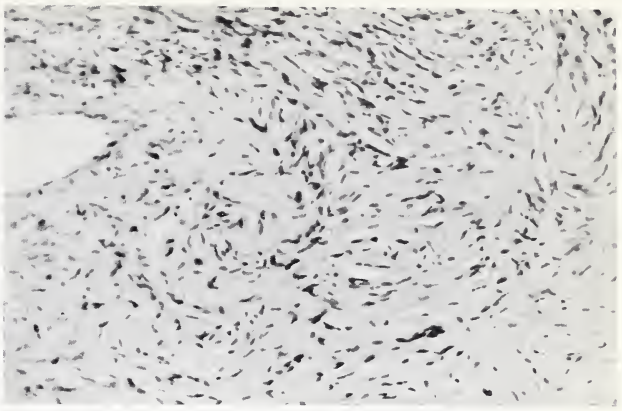

Fig. 247

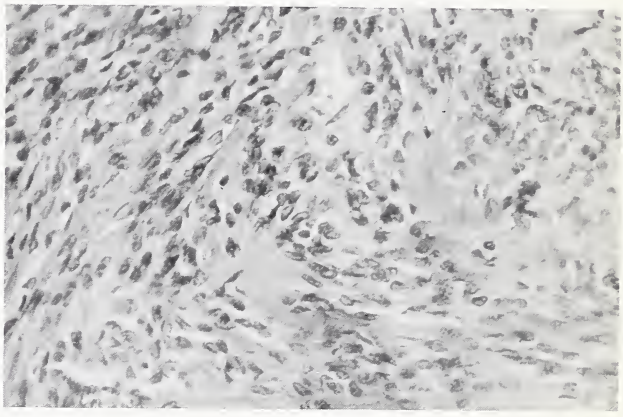

Fig. 248

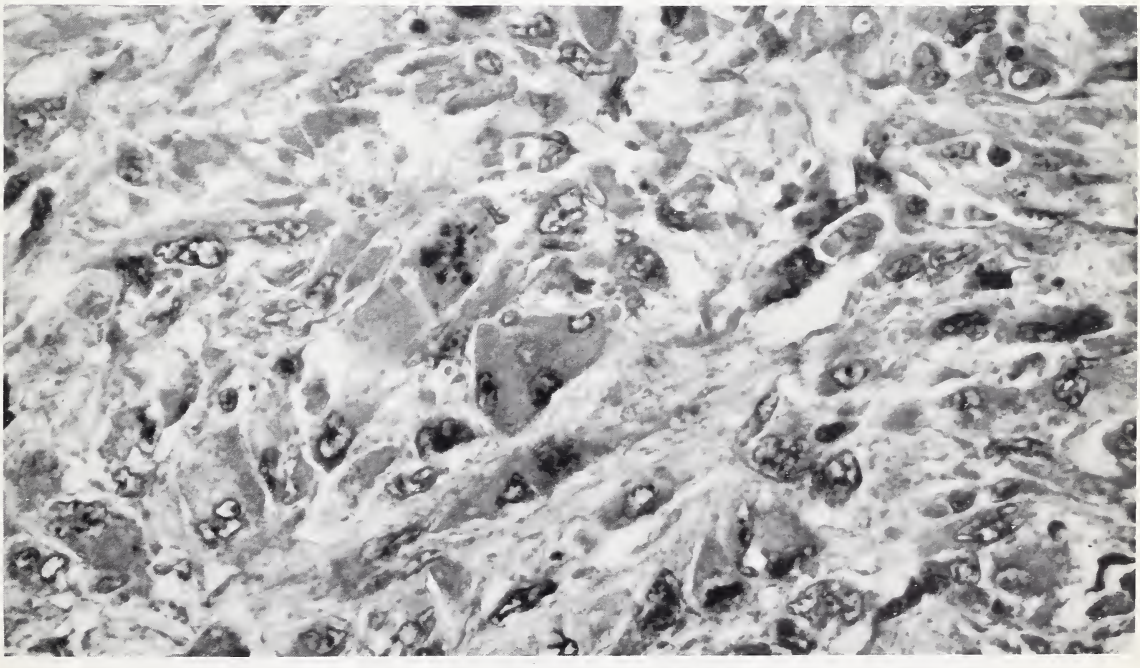

Fig. 249

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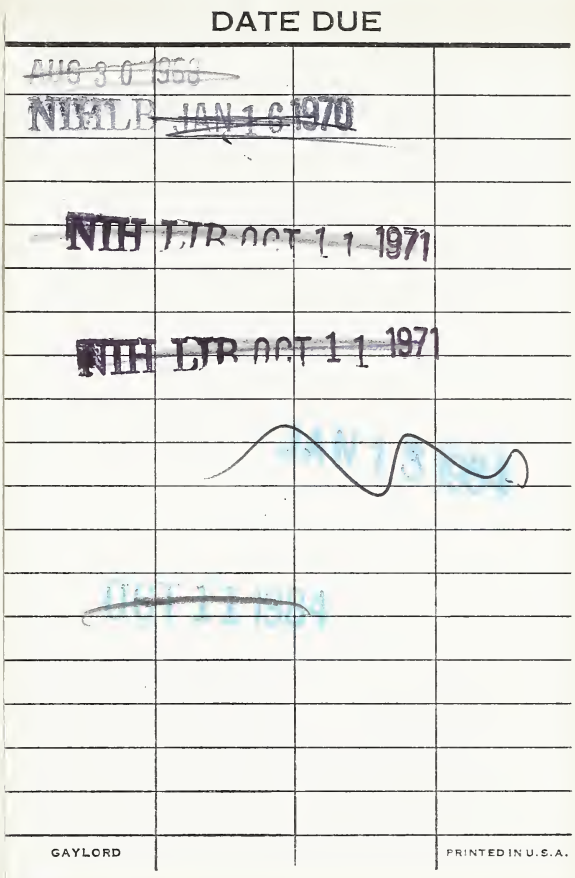

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